Evidence-Based Nephrology

Evidence-Based Nephrology

Second Edition

VOLUME I

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Preface

The synthesis of the totality of evidence in kidney disease was the original challenge we undertook when we conceived of the first edition of this evidence-based nephrology (EBN) textbook, thereby providing students of nephrology and practicing clinicians with a single convenient source of clinical evidence that had been passed through an evidence-based filter. More than 12 years have passed since the first edition, and so it is timely to revisit the challenge in the form of a second edition. The reasons for a second edition are principally three: the scale of new available data is substantial, newer methods of research synthesis have been developed, and there is a renewed focus on consumer engagement in general, including in the evaluation and management of kidney disease.

Scale of new data

Compared to the time of the first edition, the amount of new data is impressive. There are today more than 15 000 randomized controlled trials in nephrology published in approximately 30 000 reports, 11 300 more than in 2009, resulting in more confidence and precision around the estimates of intervention effects and new evidence in areas that were previously mostly evidence-free. These trials have also been summarized in systematic reviews, with over 6500 additional reviews in Medline since the first edition. Much of this new evidence is incorporated in three new sections of this textbook and multiple either new or entirely updated chapters.

Novel methods

Methods to assess the methodological quality of both systematic reviews and other study designs, including nonrandomized (case-control or cohort studies) and diagnostic test studies, have developed since the first edition. In addition, the number of syntheses of cohort studies has increased and the technique of network meta-analysis for comparing more than two interventions both directly (head to head) and indirectly (via a common comparator) has become more developed and is commonly encountered. These methods assist the summarizing and interpreting of evidence in key areas of decision-making, which is useful to patients, healthcare providers, and policy-makers.

Using these methods, organizations including the Cochrane Kidney and Transplant group and several guideline agencies have committed on a large scale to summarize the evidence and provide timely updates of established and emerging new evidence, making research findings more manageable and reliable for end users. Much of this work has been included in this edition of the textbook. We hope this will allow the end-user to both access best evidence from this diversity of resources as summarized by chapter authors and to become more familiar with how the newer techniques and resources contribute to a practice that is informed by best evidence.

Consumer engagement

Recently, there has been increasing recognition of the critical importance of engaging the end-users in research to ensure relevance and uptake. In particular there have been large-scale efforts to engage patients in all stages of research, including the evidence synthesis process and the dissemination of findings. For example, the Cochrane Kidney and Transplant group now has a patient editor, whose role includes translating scientific outputs into plain language summaries to simplify the "medical jargon" and make evidence easily accessible to people without a medical background, as well as prioritizing review topics. The Standardized Outcomes in Nephrology (SONG) initiative was launched in 2014 to establish the core outcomes to be reported in all trials in chronic kidney disease, based on a consensus among patients, caregivers, health professionals, and policy-makers. This initiative has emphasized patient-centered research and improved clinical outcomes in nephrology, ensuring that the outcomes measured and reported in clinical trials and other forms of research are relevant and meaningful to patients and increase the acceptability, transparency, and generalizability of the results in this population. New studies assessing these

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outcomes are now being developed, with advancement of knowledge which could be incorporated into this edition of the textbook.

In short, compared to the previous version published in 2009, this updated textbook includes 20 new chapters and three new sections, covering supportive care and patient-centered care and outcomes. In addition, every chapter that was in the first edition has been extensively updated. Specifically, the new textbook covers epidemiology, acute kidney injury, primary diseases of the kidney, secondary diseases of the kidney, chronic kidney disease and complications, hemodialysis, chronic kidney disease stage 5, peritoneal dialysis, supportive care, transplantation, electrolytes and acid-base disorders, and patient-centered care and outcomes for both adult and pediatric patients. This effort was undertaken by existing and new authors and section editors, whom we would like to thank for their extensive work.

Giovanni Strippoli has joined as the third co-editor of *Evidence-based Nephrology*. Altogether, we hope that we have produced an even better evidence-based nephrology tool, where each chapter provides a clear foundation of the topic that is supported by the best current evidence.

We believe that this updated textbook more broadly covers available evidence and addresses crucial clinical questions regarding the treatment and care of people with all stages of chronic kidney disease, including people undergoing any form of dialysis (hemodialysis or peritoneal dialysis), those requiring kidney transplantation, and pediatric patients.

Inherently a textbook of this nature will always manifest potential limitations. We acknowledge that a textbook is unable to collect all new evidence in real time, and, like all of healthcare internationally, the COVID-19 pandemic did impact this book, specifically the publication timelines as contributors had to contend with major challenges. The inclusion of nonrandomized studies to maximize relevance and comprehensiveness has added complexity in the methods and may lead to residual uncertainty in the estimate of intervention effects. Finally, we focused on empiric evidence for management decisions and so pathophysiological mechanisms of chronic kidney disease and its treatment were not considered in detail. We have attempted to include economic evaluations where particularly relevant for national and international management guidelines.

In the true spirit of evidence-based medicine, we hope that this edition of *Evidence-based Nephrology* will continue to push the specialty toward greater reliance on the totality of evidence and the generation and utilization of evidence that is the least biased and the most precise to inform clinical decision making. To the material detailed in all the chapters we would expect that our readers will add, through their own judicious application of evidence-based medicine principles, their local context, and incorporate their patients values and preferences, given that objective evidence is rightly only one consideration in the delivery of true patient-centered care. Additionally, a textbook like this can at best be only one of several resources for the evidence-based medicine practitioner, and should be supplemented with current methodologically rigorous and transparent clinical practice guidelines. We hope this effort will provide a core resource for the evidence-based nephrology practitioner who is otherwise limited by time constraints from researching every question that may arise daily in the care of patients.

We certainly wish that students and evidence-based nephrology practitioners will benefit from this updated edition in the search for answers to questions that arise in daily care and their ambition to deliver the best care possible.

Jonathan C. Craig
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Part 1

Epidemiology

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1

An Introduction to the Epidemiology of Chronic Kidney Disease

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Introduction

The purpose of this part of the book is to describe the epidemiology of chronic kidney disease (CKD) across the spectrum of disease, from early detection through to major complications and end-stage kidney disease (ESKD). Fundamental to this is an understanding of what defines CKD. We will therefore begin this chapter by revisiting the 2002 National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF/DOQI) guideline, which first proposed a harmonized definition of CKD based on simple laboratory markers. A tremendous amount of data has been accrued since that seminal publication, data which informed the updated CKD classification system by Kidney Disease Improving Global Outcomes (KDIGO) in 2012.

The definition and staging of CKD has generated debate and controversy among the nephrology community. There is confusion surrounding the definition and the classification system. The former is an important, inclusive, and objective definition to describe the state of kidney function and structure which is associated with disease. The latter describes the severity of disease and risk associated with two parameters: level of estimated glomerular filtration rate (GFR) and degree of albuminuria. The classification of CKD is underpinned by the risk of a series of clinical outcomes. The key outcomes in this context are progression to ESKD, cardiovascular, and all-cause mortality. Other outcomes include acute kidney injury (AKI), hospitalization, cardiovascular events, and infections. This chapter provides an overview of the risk relationships between CKD and these first three well-studied outcomes. We also highlight some of the more controversial aspects of the CKD paradigm: the definition of CKD in older individuals, and strengths and limitations of different filtration markers and GFR estimating equations. These important issues continue to be discussed and debated within the nephrology community. However, it should be acknowledged that patients with kidney disease are looked after by other healthcare providers, including primary care physicians, cardiologists, and gerontologists. Thus, the framework for diagnosis, staging, and risk stratification of patients with kidney disease must be clear and well-communicated to all stakeholders. This is especially pertinent in developing countries, where our understanding of the epidemiology of kidney disease and its risk factors is more limited.

The subsequent chapters in this part expand on these concepts and provide the reader with an up-to-date review of the state of knowledge of the epidemiology of kidney disease. Chapter 2 describes the variety of surveillance mechanisms currently utilized for CKD and ESKD, along with the challenges of obtaining accurate data from around the world. The importance of early detection of CKD and the evidence for population-level screening is discussed in Chapter 4. Chapters 3 and 5 provide an evidence-based approach to prognostication for progression of CKD and the risk of important clinical outcomes such as cardiovascular disease and mortality. Finally, the emerging literature regarding the burden of CKD in disadvantaged populations is described in Chapter 6. Throughout these chapters, a standardized nomenclature for CKD is used to frame the discussions. Hence, that is where we begin this introduction.

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Definition of CKD

In 2002 NKF-KDOQI published a guideline proposing a new paradigm for the classification and evaluation of kidney disease [1, 2]. This conceptual framework (Figure 1.1) addressed an unmet need in nephrology: the early identification of patients at risk of either developing kidney disease or progressing to more advanced stages of disease. The NKF-KDOQI working group suggested a new classification system that could categorize the severity of an individual's kidney disease, irrespective of etiology, using simple laboratory parameters. One of the most significant contributions of this work was the harmonization of nomenclature for kidney disease [3]. The term "chronic kidney disease" and its stages would supplant ambiguous terminology such as "azotemia," "predialysis," or "renal insufficiency" [4]. The original guideline has had a major impact over the last 15 years or so by facilitating collaborative research endeavors, standardizing clinical and laboratory practices, and informing health policy.

The definition of CKD was further refined by the KDIGO working group in the 2012 guidelines, and is the one used in contemporary clinical practice. KDIGO defines CKD as abnormalities of kidney structure or function, present for at least 3 months, with implications for health [5]. CKD can thus be defined by markers of kidney damage and/or markers of reduced kidney function. GFR is considered the best metric of kidney function and is estimated from the serum concentration of a circulating filtration marker such as creatinine or cystatin C. CKD can be diagnosed by GFR criteria alone if an individual has at least two estimates of GFR below 60 ml/min/1.73 m^2 at least 3 months apart. Even in the presence of "preserved" kidney function (GFR ≥ 60 ml/min/1.73 m^2), CKD can be diagnosed in the presence of persistent urinary abnormalities such as albuminuria, hematuria, or evidence of tubular dysfunction. In the absence of any of these factors, an individual can be diagnosed as having CKD if they have a structural abnormality identified on imaging tests, for example polycystic kidney disease, or a histopathological abnormality such as tubulointerstitial disease.

KDIGO proposed a standardized approach to the classification of CKD based on the cause of disease (C), level of GFR (G), and amount of albuminuria (A), the CGA system. The classification and staging of CKD can be done independent of cause, but the guidelines clearly recognized the importance of attempting to ascertain the etiology of CKD. Statements within the guidelines acknowledge the importance of interpreting the GFR and albuminuria results in the context of an underlying cause, as the specific cause may influence the risk or anticipated rate of disease progression. In many cases, however, the cause is unknown or can only be speculated upon based on the presence or absence of key risk factors such as diabetes or hypertension. For many patients a kidney biopsy remains the only means of establishing a firm diagnosis, although recent advances in molecular diagnostics have the potential to overcome this barrier [6]. The clinical focus on GFR and albuminuria for CKD staging is based on iterative studies demonstrating that both parameters are powerful predictors of clinical outcomes. The cross-classification of GFR and albuminuria stages provides a categorization of an individual's risk status (Figure 1.2). The synergistic effect of both risk markers is reflected in the fact that individuals with a combination of reduced GFR and a high degree of albuminuria are at greatest risk for ESKD. It is also evident from this risk classification that the presence of albuminuria is a strong risk factor for ESKD even if the GFR is normal. The thresholds of GFR and urinary albumin to creatinine ratio (ACR) that are used to establish the stage of CKD are based on large population-based studies examining the association between both markers and hard clinical endpoints.

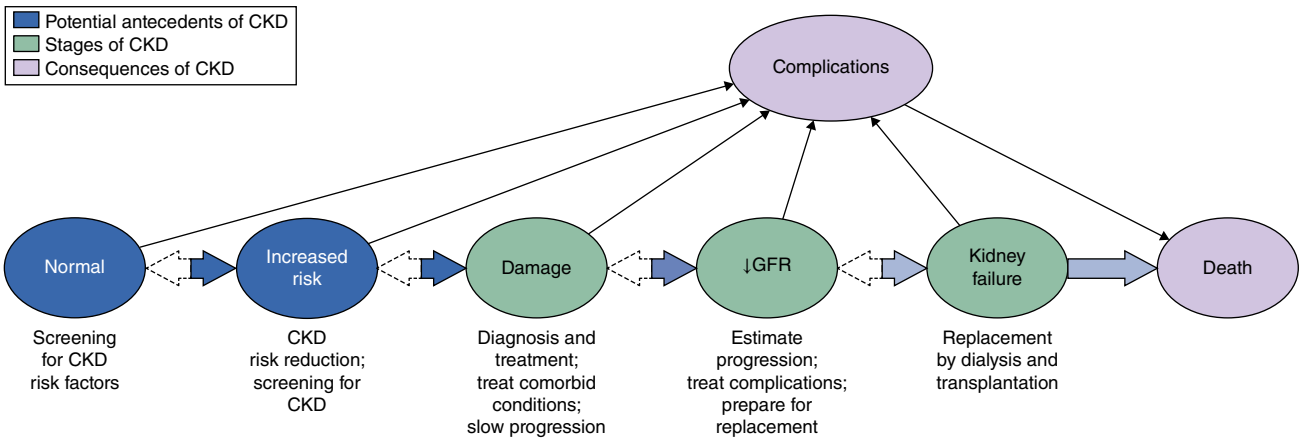

Figure 1.1 Conceptual paradigm for chronic kidney disease. CKD, chronic kidney disease; GFR, glomerular filtration rate.

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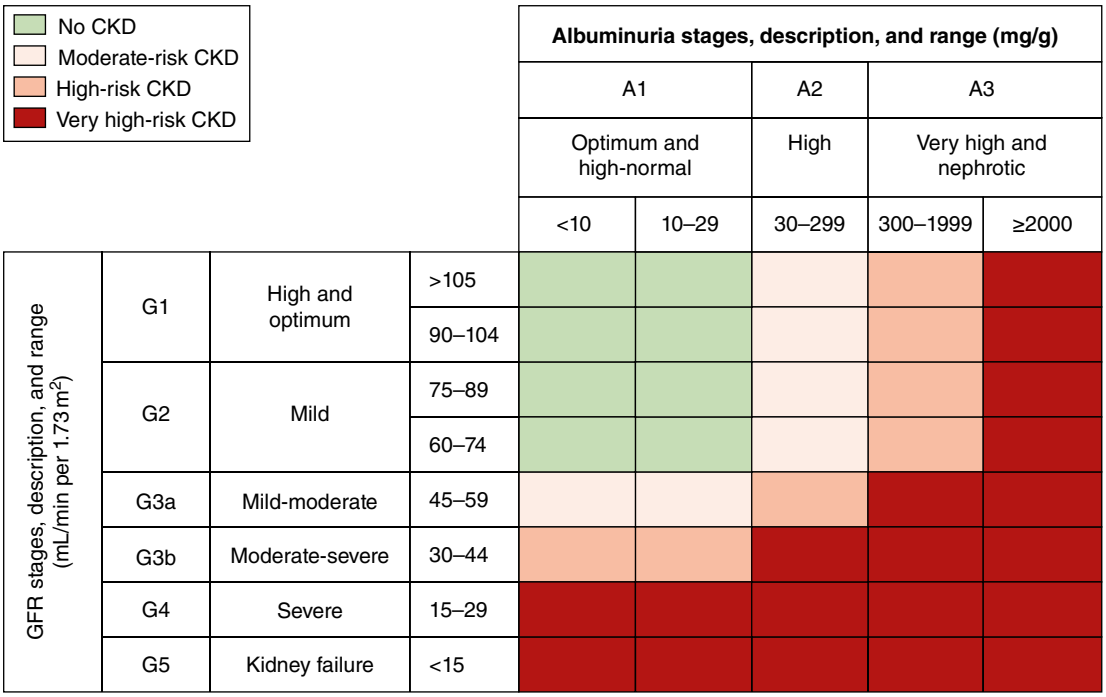

Figure 1.2 Cross-classification of glomerular filtration rate and albumin to creatinine ratio stages with respect to risk of clinical outcomes. CKD, chronic kidney disease; GFR, glomerular filtration rate.

CKD and Outcomes

Contemporary data pertaining to CKD and risk of clinical outcomes come predominantly from the CKD Prognosis Consortium (CKD-PC), an international team of investigators from over 70 cohorts worldwide [7]. These cohorts represent individuals from the general population, those at high risk of vascular disease, as well as individuals with established kidney disease. CKD-PC investigators have consistently demonstrated higher risk of adverse outcomes associated with reduced eGFR and/or increased ACR, independent of demographic and clinical characteristics.

All-Cause Mortality

In general population cohorts, both a reduced eGFR and an elevated ACR have been associated with higher risk of all-cause mortality [8]. The risk relationship between eGFR and mortality tends to be J-shaped, in that individuals with "high" eGFR (>95 ml/min/1.73 m^2) also appear to have an increased mortality risk. This is most likely explained by malnutrition or low muscle mass (and therefore lower creatinine generation) in the setting of severe illness. The association between albuminuria and mortality tends to be broadly linear. In one large meta-analysis, risk of death was increased by 20%, 63%, and 122% for ACR values of 10, 30, and 300 mg/mg compared to an ACR of 5 mg/mg [9]. CKD, whether defined by eGFR or ACR criteria, is associated with substantial reductions in life expectancy [10, 11].

Cardiovascular Events

CKD has been identified as a risk factor for several cardiovascular outcomes, including coronary events, heart failure, stroke, peripheral arterial disease, and cardiovascular mortality [12–14]. The risk of myocardial infarction associated with CKD may be at least as high as the risk associated with diabetes [15]. The presence of CKD is also a risk factor for recurrent coronary events, with a magnitude of risk that is higher than traditional cardiovascular risk factors such as smoking [16]. These findings suggest that CKD should be regarded as a coronary heart disease risk equivalent [17]. Data from CKD-PC quantified the risk of cardiovascular mortality for eGFR and ACR categories in 266 975 individuals with known cardiovascular risk factors [18]. An increased risk of mortality was evident below a threshold eGFR of 45 ml/min/1.73 m^2. Even small increases in albuminuria were associated with higher cardiovascular risk. Individuals with CKD often have other comorbidities such as hypertension and diabetes, both of which are also highly prevalent in the general population. The risk of cardiovascular disease associated with CKD may be attributable to shared risk factors in people with

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these conditions. This specific question was addressed in two large meta-analyses which demonstrated that the higher observed risk of cardiovascular mortality in individuals with reduced eGFR and/or increased ACR was evident in those with and without diabetes and hypertension [19, 20]. The underlying mechanism driving poor cardiovascular outcomes in people with CKD is multifactorial and continues to be an area of intensive research efforts. Despite consistent evidence of higher cardiovascular risk, patients with CKD are often underinvestigated and undertreated. One of the reasons for this is the under-representation of patients with kidney disease, particularly advanced disease, in clinical trials. It is not known if interventions which have been shown to improve outcomes in people without kidney disease will have the same benefits and adverse effect profiles in people with CKD. This knowledge gap needs to be urgently addressed. The strength of evidence for cardiovascular risk prediction is expanded upon in Chapter 5.

Progression to ESKD

The risk of ESKD is dramatically increased in the setting of reduced eGFR and/or high-grade albuminuria. In the general population, this increased risk becomes apparent below an eGFR of 75 ml/min/1.73 m^2 and increases in exponential fashion at the lower end of eGFR [21]. In CKD cohorts, each 15 ml/min/1.73 m^2 reduction in eGFR below 45 ml/min/1.73 m^2 confers an approximate sixfold higher risk of ESKD [22]. Similar to cardiovascular and mortality outcomes, the risk relationship between albuminuria and ESKD appears to be more linear. The consistency of the associations between eGFR, ACR, and ESKD risk facilitated the creation of the Kidney Failure Risk Equation, which calculates the probability of progressing to ESKD at specific time points based on an individual's age, sex, eGFR, and ACR [23]. Risk prediction models and risk factors for disease progression are comprehensively evaluated in Chapter 5.

GFR Estimating Equations and Risk

Indirect quantification of GFR, via clearance of an exogenous filtration marker, is the gold standard for measurement of GFR but is rarely performed in practice outside of specific clinical indications. The large-scale population studies described above would not have been feasible without a method for calculating an estimate of GFR. A number of GFR estimating equations have been developed and validated for use in clinical and research settings. In contemporary practice, the most widely used is the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [24]. CKD-EPI has a number of advantages over its predecessor, the Modification of Diet in Renal Disease (MDRD) equation [25, 26]. These include a more diverse derivation cohort which included people with and without kidney disease, less bias in the upper range of GFR (≥60 ml/min/1.73 m^2), and superior risk discrimination for hard outcomes [27]. A significant limitation of the CKD-EPI cohort was the under-representation of individuals over the age of 70 years. An alternative GFR estimating equation for this demographic was developed by the Berlin Initiative Study (BIS) investigators [28].

There is a trade-off in the use of any GFR estimating equation: the widespread ease of their use versus the uncertainty in estimation. Some of this uncertainty is due to inherent variability in the regression models that generated the estimates, most notably at the higher range of GFR where the models tend to perform less well. More importantly, creatinine generation can vary widely between individuals due to differences in muscle mass and dietary protein intake [29]. Several alternative filtration markers have been studied, but none have managed to replace creatinine as the marker of choice in routine clinical practice. One such alternative is cystatin C, a 13 kDa protein that is produced by all nucleated cells and freely filtered at the glomerulus. Although cystatin C is a better predictor of measured GFR than creatinine [30], the adjustment of creatinine for body composition using the variables age, sex, and race largely overcomes this deficit [31]. Where the two markers differ is with respect to risk stratification. GFR estimated from cystatin C is a stronger and more consistent predictor of clinical outcomes compared to GFR estimated from creatinine [32]. It should be noted that cystatin C also has "non-GFR" determinants, including adiposity and inflammation, themselves recognized as risk factors for adverse clinical outcomes such as cardiovascular disease [33, 34].

Risk Factors for CKD

Hypertension

Hypertension is estimated to affect 1.13 billion adults globally, with an age-standardized prevalence of 24.1% in men and 20.1% in women [35]. Hypertension is highly prevalent among individuals with CKD, especially in more advanced stages of disease. The kidney is a vulnerable organ to the effects of sustained elevations in blood pressure (BP), and hypertension is a risk factor for both incident CKD and progression to ESKD [36, 37]. In the CKD population, the relationship between BP and cardiovascular outcomes and mortality tends to be J-shaped, suggesting higher risk of

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adverse outcomes with high and low BP [38–40]. This finding could be explained by underlying cardiac disease in individuals with low BP, which may be subclinical and not optimally captured in studies [41]. Blood pressure is a dynamic measure of health, and what we consider as the mean or "usual" BP may not be telling the whole story [42]. Variability in ambulatory BP recordings is a strong predictor of major cardiovascular events such as stroke, independent of the mean BP [43]. Similarly, large variability in visit-to-visit BP has been identified as a risk factor for adverse CKD outcomes [44]. Impaired stabilization of BP during postural change has recently been highlighted as a potential contributor to adverse outcomes [45, 46] and is also associated with CKD [47, 48]. These studies illustrate the complexity of the relationship between changes in blood pressure and their effects on the kidney. Our understanding of hypertension in CKD is further hampered by the under-representation of CKD patients in large clinical trials, such that optimal management of hypertension in patients with kidney disease continues to be debated.

Diabetes Mellitus

Diabetes continues to be a major contributor to CKD and associated outcomes. While the rates of diabetes-related complications including ESKD have reduced over time in relative terms, the prevalence of diabetes has continued to increase such that the absolute rates of complications are expected to continue to rise [49, 50]. The risk of kidney disease attributable to diabetes in large population studies is subject to misclassification. Individuals with diabetes tend to have a higher prevalence of other CKD risk factors such as obesity and hypertension. As such, in the absence of a tissue diagnosis the cause of their kidney disease cannot be definitively ascribed to diabetes. This limitation has historically hampered efforts to understand mechanisms in diabetic kidney disease and has motivated initiatives like the Kidney Precision Medicine Project [51]. The landscape of diabetic kidney disease could change dramatically with the advent of sodium-glucose cotransporter type 2 (SGLT2) inhibition as a therapeutic target. Clinical trials of SGLT2 inhibitors have demonstrated improvements not only in glycemic control, but also in cardiovascular and renal endpoints [52, 53]. These effects may be mediated through beneficial changes in blood pressure, glomerular hemodynamics, body weight, and uric acid [54].

Acute Kidney Injury

AKI may be defined as a transient reduction in kidney function, detected clinically by a change in creatinine or a decrease in urine output over a specified time interval [55]. AKI is associated with increased risk of morbidity and mortality, particularly from cardiovascular disease [56, 57]. Severe AKI necessitating temporary dialysis is a risk factor for long-term development of ESKD [58]. On the other end of the spectrum, apparently "mild" injury has been associated with increased risk of developing CKD, especially if recovery is slow and even if kidney function ultimately returns to its baseline value after the event [59, 60]. In some patients the relationship between AKI and CKD is bidirectional [61]. A diminished GFR and albuminuria are cardinal risk factors for AKI [62–64], which in turn may contribute to progression of underlying CKD [65]. The importance of AKI as a risk factor for CKD progression, and methods to identify those at risk of progression after an AKI event, are discussed in detail in Chapter 3.

Prevalence of CKD

Several studies have provided estimates of CKD prevalence from different jurisdictions around the world, with estimates between 8% and 16% [66]. In the United States, prevalence data come from a series of national surveys called the National Health and Nutrition Examination Survey (NHANES), a stratified cluster probability sample of US adults. The application of survey weights provides representative estimates of disease prevalence. Data from NHANES suggest an overall prevalence of CKD in the United States of 13%, with the majority of individuals with CKD having mild to moderate reductions in eGFR (30–59 ml/min/1.73 m^2) and less than 1% having more severe disease [67]. European prevalence data from various cohorts were recently published from the European CKD Burden Consortium [68]. In keeping with US data, the investigators documented an overall high prevalence of CKD. This group also found substantial heterogeneity in the methodology of included studies, for example different definitions of CKD using eGFR, ACR, or both, varying sample response rates, use or nonuse of a sampling frame, and lack of standardization of assays for creatinine [69]. This heterogeneity poses a significant challenge when seeking to understand the true prevalence of CKD and is discussed further in Chapter 2.

An important, but perhaps under-appreciated, source of bias in prevalence studies is misclassification of CKD stage based on a single measurement of eGFR or ACR. While it is understandable from a feasibility perspective that large population studies would not perform a second test of eGFR and ACR after 3 months to fulfill the chronicity criterion of the KDIGO definition, recent studies have demonstrated the potentially large degree of

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misclassification that can arise from a single test [70]. The same is true of prognostic studies, yet the implication of misclassification in that context is unclear. The amount of albumin excretion can vary significantly within an individual [71], while eGFR can be affected by a host of factors related to creatinine generation such as changes in diet and body composition [72].

CKD in the Developing World

The bulk of our knowledge of CKD epidemiology comes from studies undertaken in high income countries with sufficient data infrastructure to reliably estimate prevalence and incidence rates. The majority of the world's population lives in middle-income and low-income countries, where our understanding of the burden of kidney disease is sorely lacking. What is evident from the available data is that this burden is expected to increase dramatically in the coming decades due in large part to growing rates of diabetes, obesity, and hypertension in the developing world [73]. Infection continues to be a major driver of CKD in these countries, including the many and varied renal manifestations of infection with human immunodeficiency virus [74, 75]. A current area of intensive research efforts is chronic kidney disease of unknown etiology (CKDu), a condition highly prevalent among young and middle-aged male agricultural and plantation workers. Affected individuals lack traditional risk factors for kidney disease, and a number of pathogenic factors have been hypothesized including heat stress, dehydration, and exposure to heavy metals [76]. The final common pathway appears to be interstitial inflammation and fibrosis, as suggested in a biopsy series from Central America [77]. Similarly, in a large series from Sri Lanka, half of patients who underwent kidney biopsy had evidence of a primary tubulointerstitial kidney disease [78]. Our knowledge of kidney disease epidemiology and appreciation of underlying mechanisms in developing countries is in its infancy. The multiple and diverse challenges that need to be overcome in order for us to enhance our understanding of, and effect meaningful change in, kidney disease burden among disadvantaged populations are discussed in detail in Chapter 6.

Kidney Disease as a Global Public Health Priority

The importance of understanding the epidemiology of CKD is underscored by the impact of CKD on health at a population level around the world [79]. The magnitude of this impact, and how CKD compares to other chronic conditions, has been quantified by the Global Burden of Disease (GBD) studies. Since 1992, the GBD investigators have ranked individual diseases based on the number of global deaths and disability-adjusted life years (DALY) attributable to each disease [80]. DALY is a time-based measure that combines years of life lost due to morbidity and premature mortality, and was developed with the aim of informing cost-effective analysis and public health policy. The scope of the GBD study continues to expand since its first report in 1990. The 2015 iteration reported data for 300 diseases in 195 countries [81]. Those 25 years have witnessed an ominous trend for CKD, which is now the 12th leading cause of death worldwide compared to a ranking of 27th in 1990 [82]. Mortality attributable to CKD is an estimated 1.2 million deaths, representing a rate of 19.2 per 100 000 persons per year. Cardiovascular disease is the biggest contributor to that mortality rate [83]. Worryingly, this mortality rate may be an underestimate, given that CKD is not always listed as a cause of death, for example in the setting of diabetes [84]. In keeping with mortality data, CKD is also a major contributor to DALYs. In some parts of the world, including Latin America and South-East Asia, CKD is currently ranked in the top 10 for DALYs [81, 82]. It is evident, therefore, that the impact of CKD on population health is considerable, and growing.

CKD in Specific Subgroups

Older Adults

The diagnosis of CKD in older adults has been one of the more controversial aspects of the CKD classification system. Measurement studies from decades ago demonstrated an age-related decline in GFR. Similar findings have been shown in contemporary large population studies using estimated GFR. For example, in a cross-sectional study from the Netherlands, the expected decline in eGFR was 0.4 ml/min/1.73 m^2 per year of age among apparently healthy adults with no renal or cardiovascular risk factors [85]. The current eGFR diagnostic threshold of 60 ml/min/1.73 m^2, without albuminuria or other evidence of kidney damage, captures a substantial proportion of older community-dwelling adults as having CKD. Among individuals over 70 years of age, prevalence estimates have been as high as 40% [67, 68]. The majority of older adults with CKD have relatively modest reductions in eGFR (45–59 ml/min/1.73 m^2). It has been argued that the threshold to define CKD in otherwise healthy adults over the age of 60 years should be lowered to an eGFR < 45 ml/min/1.73 m^2 to avoid overdiagnosis and disease-labeling in this subpopulation [86]. Central to this viewpoint is the recognition of a mismatch between a seemingly high prevalence of

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disease and low incidence of organ failure, partly explained by competing mortality from other age-related comorbidities [87]. On the other side of the debate, investigators point to the risks associated with CKD in older people [88]. A large meta-analysis leveraging data from over 1 million participants from 33 general population and high-risk (of vascular disease) cohorts specifically addressed this question by examining the interaction of age and kidney parameters for the risk of ESKD and mortality [89]. This study demonstrated that, while the relationship between eGFR/ACR and outcomes varied by age, a reduced eGFR or increased ACR was associated with increased risk of ESKD and mortality across all age categories. In addition to hard outcomes, older adults with CKD are also at higher risk of more proximal outcomes. Several studies have identified CKD as an independent risk factor for reduced physical performance, frailty, and cognitive impairment [90–92]. Thus, the notion of changing the threshold for the definition of CKD based on age alone is not substantiated with data; and would be analogous to changing thresholds for other diseases such as diabetes or hypertension based on age. The implications of a diagnosis of CKD, potential interventions, and targets of therapy may differ between older and younger individuals, but the actual definition of CKD is not age-dependent.

Sex Differences in Kidney Health and Outcomes

The prevalence of CKD appears to be higher in women compared to men, estimated at 16.5% and 13%, respectively, in the United States [93]. Possible reasons for this discrepancy include a shorter life expectancy in men and potential misclassification of CKD using GFR estimating equations in the general population [94]. On the other hand, proportionately more men start renal replacement therapy owing, at least in part, to faster decline in kidney function compared to women. The association between eGFR and albuminuria and hard outcomes is consistent in both sexes, although the slope of the relationship with mortality may be steeper in women [95]. While understudied, women also have unique risk factors for kidney disease, including pregnancy complications and higher incidence of systemic autoimmune disease [96].

Race/Ethnicity

The impact of race on the incidence and severity of kidney disease has been most comprehensively studied in the United States. It has long been recognized that African American patients with kidney disease have a higher-risk profile, evidenced by a substantially increased prevalence of ESKD compared to other racial groups. Recent landmark genetic studies have shed light on this phenomenon. Mutations in the apolipoprotein L1 (APOL-1) gene, found exclusively in individuals of recent African descent and protective against trypanosomal infection, are strongly associated with nondiabetic kidney disease, including that attributed to idiopathic focal segmental glomerulosclerosis and hypertension [97, 98]. APOL-1 variants have also been shown to confer a higher likelihood of CKD progression [99]. The potential influence of race and ethnicity on kidney outcomes around the world is not well understood due to a lack of data infrastructure and high-quality studies (see Chapter 2). While prevalence rates of CKD vary by race, data from the CKD-PC suggest that the risk relationships between reduced eGFR, albuminuria, and clinical outcomes are consistent across racial groups [100]. On a broader level, the use of race in medicine has come under increasing scrutiny, particularly the inclusion of race in diagnostic and treatment algorithms [101]. From a nephrology perspective, there is a growing concern that the inclusion of a race coefficient in GFR estimation and in the evaluation of organ donors is disadvantaging Black patients [102]. In 2021, a task force jointly created by the National Kidney Foundation and American Society of Nephrology recommended the implementation of a new race-free GFR estimating equation published by the CKD-EPI investigators [103, 104]. The implications of this for clinical decision-making and health policy are currently being evaluated, but it is hoped that this change will go some way towards achieving equity for all patients with kidney disease.

Knowledge Gaps and Future Directions

Our knowledge and understanding of kidney disease epidemiology has grown exponentially over the last 15 years, which is testament to the intensive and rigorous research efforts of the international nephrology community. Inevitably, as more data accrue more questions will arise. The CKD classification system provided a common platform from which to start from. There is now a need for improved understanding of variability in outcomes on the individual patient level to inform shared decision-making based on individualized risk-stratification. Integral to this is accurate definition of the disease phenotype, moving from assumptive to definitive diagnosis through molecular diagnostics or by lowering the threshold for kidney biopsy in "common" disorders. The data that currently inform clinical practice have been almost exclusively acquired from studies

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in developed countries with an appropriate data infrastructure and access to nephrology care, including renal replacement therapy. This data cannot be extrapolated to the majority of the world's population in developing countries where susceptibility to kidney disease, access to care, and choice of therapies are fundamentally different. The subsequent chapters in this part expand on these and other important issues, as we strive to meet the current and future challenges of kidney disease around the globe.

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2

The Surveillance and Burden of Chronic Kidney Disease

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Surveillance of CKD

The World Health Organization defines surveillance as the "continuous, systematic collection, analysis and interpretation of health-related data for the planning, implementation and evaluation of public health practices." In terms of chronic kidney disease (CKD), surveillance refers to activities aimed at providing key information on the burden of, and risk factors for, CKD with a view to reducing variation in, and improving the quality of, care processes and health outcomes associated with the condition [1]. Information from CKD surveillance can potentially be used to guide resource planning and implementation of medical and public health measures along with informing health policy. Optimization in the management of CKD could prevent progression to kidney failure and the need for dialysis and transplantation [2] as well as potentially reducing the burden of hospitalization from nonrenal complications (e.g. cardiovascular disease) [3].

Potential Benefits of CKD Surveillance

While there is insufficient evidence to support the efficacy of screening for CKD among the general population [4–6], consistent evidence suggests that presence of proteinuria or reduced estimated glomerular filtration rate (eGFR) is strongly associated with end-stage renal disease (ESRD), cardiovascular, and all-cause mortality in population-based studies [7–10]. Equations that predict progression of CKD have been validated in high-income settings [11, 12]. The absolute numbers reaching ESRD are small, but those who do go onto need renal replacement therapy (RRT) benefit from early referral to specialist services [13]. However, the best approaches to identify this group remain the subject of ongoing research [14–16]. Combining testing for CKD with screening for other noncommunicable diseases or risk factors means that surveillance for CKD in high-risk populations may be the most efficient and effective approach [1, 17]. These targeted populations include those with hypertension, diabetes, and cardiovascular disease [18–21]. Aside from benefits at the patient level, estimates of the projected incidence of ESRD and dialysis needs in a local population are key for health services planning. Furthermore, understanding prevalence of CKD in a population may have broader implications given the relationship between CKD and hospitalizations from multiple causes such as cardiovascular events, acute kidney injury (AKI), and infections [3].

For patients with ESRD (sometimes also including those with the advanced stages of CKD), many countries have registries where treatments and outcomes are monitored [22]. As well as providing data on the incidence of RRT in a particular population, these registries aim to guide management and improve care processes toward better health outcomes [23, 24].

Types of CKD Surveillance

Surveillance systems are generally divided into passive and active approaches. A passive surveillance system relies on data routinely collected in current practice. These include death registries, hospital records, and primary care records (Table 2.1). These types of routine data sources are efficient and powerful tools in CKD surveillance, particularly where

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Table 2.1 Types of passive surveillance for CKD.

Passive surveillance	Potential indicators	Numerator	Denominator	Generalizability	Potential strengths	Potential limitations	Potential biases
Death registries	Mortality rate Age- and sex-specific mortality rate SMR	Deaths attributed to CKD/ESRD	Population covered by death registration	Local and national level International comparisons (SMRs)	Resource efficient Explore geographical variations	Attributing deaths to CKD/ESRD Disaggregation by area/populations	Coverage and validity of death certificates
Dialysis registries and transplant registries	Incidence of ESRD Age-specific incidence of ESRD Standardized incidence of ESRD	Patients with ESRD starting RRT because of ESRD (requiring dialysis for 90 days or more)	Population with access to dialysis and transplantation	Patients with coverage for ESRD	Resource efficient Explore geographical variations	Not representative of burden of CKD (untreated ESRD) Obtaining patient-level data Limited data on treatment and patient outcomes	Coverage of RRT Access to care Competing mortality
Hospital records (admissions data)	Prevalence of CKD and/or ESRD	Patients diagnosed with CKD and/or ESRD	Patients who are in hospital care	Patients who seek or are referred to hospital care	Availability of kidney (bio) markers Availability of treatment and patient outcome data	Not representative of true population prevalence/incidence of CKD Completeness of information	Classification based on eGFR and/or ICD 10 Influence of AKI on results Creatinine calibration and method used Referral patterns from primary care Competing mortality
Primary care records	Incidence and prevalence of CKD and/or ESRD	Patients diagnosed with CKD (from kidney function measures)	Patients in outpatient/primary care	People who are screened/attend checkups or present for outpatient care	Detection of early stages of CKD	Not representation of true population prevalence/incidence of CKD (rather among those who regularly get renal function tests) Completeness of information	selection bias due to self-presentation or volunteer of community population Classification based on eGFR and ICD 10 Single measurement or multiple measure for diagnosis of CKD Influence of AKI on results Laboratory calibration issues

AKI, acute kidney injury; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; ICD 10, International Classification of Diseases-10; RRT, renal replacement therapy; SMR, standardized mortality rate.

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laboratory test results are available in parallel to clinical data. Outputs such as attributable deaths from CKD, and prevalence or incidence of CKD can be derived. However, there are important limitations to these datasets which mostly surround data quality, coverage, and comprehensiveness. These limitations will vary substantially both between different types of electronic health records and between different health systems. Specifically, variation in access to healthcare in some settings may lead to major issues with the representativeness of any estimates of disease burden, therefore the interpretation and generalizability of the conclusions derived from these data sets requires a clear understanding of the context and ascertainment methods within each system.

Active surveillance systems, such as national surveys or outreach testing in high-risk populations, are often more resource intensive than passive surveillance systems. With an active system the accuracy of the diagnosis of CKD may be improved and a wider range of patient factors, treatment, and health outcomes may potentially be explored. However, with the exception of population-based surveys, these data will not provide a measure of the population prevalence of CKD (Table 2.2).

In reality, most comprehensive health systems will undertake a variety of surveillance approaches using different data sources. Typically these might include death certification data, a dialysis and transplant registry, electronic health record-based surveillance and targeted outreach in high-risk groups. Indeed unexpected differences in estimates of disease burden or outcomes from these different sources may in turn provide key information about population coverage and patient care pathways within or between regions.

Challenges of Surveillance for CKD

Surveillance approaches have different challenges and limitations. Understanding these is key to the interpretation of surveillance outputs as well as finding methods to mitigate these problems. Any form of CKD surveillance should provide meaningful data as to whether burden of disease is increasing, decreasing, or stable in a population and many outputs can also be used to detect differences between populations.

Cross-sectional Surveys of eGFR

Even an imperfect surveillance method, which misclassifies an individual as to whether they have CKD, might still be useful to detect meaningful differences in CKD prevalence between populations or changes of CKD prevalence over time within a population. This is the basis of a number of single time point, or snapshot, approaches quantifying the prevalence of reduced eGFR to monitor CKD at population level, examples include the National Health and Nutrition Examination Survey (NHANES) [25] and the Health Survey for England [26]. Although the single time point measurement in a survey participant does not meet criteria for CKD per se, as chronicity is not demonstrated, conclusions can still be drawn about CKD prevalence, assuming the methods used (at different points or in different regions if comparing populations) remain the same and survey nonresponse is appropriately dealt with.

Registries of Patients Receiving RRT

Many health systems will use incidence of RRT as a measure of CKD burden. However, there are two important limitations in using this measure. First, it is based on the assumption that all patients with ESRD can access dialysis or transplantation. Across the world there are inequalities in accessing care [27] and even in Europe substantial variations exists [28]. Furthermore, health system incentives may influence the numbers starting RRT. Second, in an attempt to capture those receiving RRT due to CKD rather than AKI many registries only collect data on patients who have received dialysis for a minimum duration, for example 90 days. This means that all those patients who started dialysis because of ESRD but died within a 90-day window are not included in these estimates, potentially leading to an underestimate of disease burden.

CKD Outreach Screening

Although the use of outreach approaches to detect CKD in populations has the advantage that it can be combined with initiatives to improve the awareness of CKD, estimates of disease burden from this type of work will be critically dependent on who presents for testing and hence potentially misleading. This bias may drive estimates higher or lower, for example it may be that the more health-conscious members of the population are captured ("the worried well"), who are less likely to have kidney problems. Alternatively, those who have risk factors for, or family members with, CKD, might seek the opportunity for kidney function testing that may otherwise be difficult to access. Hence, any estimate of disease burden that does not include a representative sample of the source population of interest (best ensured by random sampling) needs to be treated with caution and may not provide useful insight into the true prevalence of CKD or trends over time in disease burden.

Routine Health Records

Passive systems utilizing available data can have many of similar problems to active approaches, in that the interpretation of the data is dependent on the source population,

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Table 2.2 Types of active surveillance for CKD.

Active surveillance	Potential indicators	Numerator	Denominator	Generalizability	Potential strengths	Potential limitations	Potential biases
National surveys (population-based studies)	Prevalence of CKD and/or ESRD	Participants diagnosed with CKD (from kidney function measures)	Random/ stratified sample of population targeted by survey	Population targeted by survey	Representative of true population incidence and prevalence of CKD in population targeted by survey	Requires sampling frame, or enumeration of population Obtaining resources and Implementation of fieldwork	Nonresponse bias
Clinic/hospital-based surveys (testing of patients not routinely tested)	Prevalence of CKD and/or ESRD	Participants diagnosed with CKD (from kidney function measures)	Hospital/clinic population attending clinic	Self-presenting or population eligible for attending hospital clinic	Completeness of kidney (bio)markers Completeness of treatment and patient outcomes data	Not representation of true population prevalence/incidence of CKD	Selection bias due to self-presentation or healthcare access Nonresponse bias
Outreach testing	Prevalence of CKD and/or ESRD	Participants diagnosed with CKD (from kidney function measures)	Selected reporting populations, often volunteers	Prevalence of CKD in selected populations	Completeness of kidney (bio)markers Completeness of treatment and patient outcomes data	Not representation of true population prevalence/incidence of CKD	Selection bias due to self-presentation or volunteer of community population
Occupational or workplace-based surveys	Prevalence of CKD and/or ESRD	Participants diagnosed with CKD (from kidney function measures)	Random sample/stratifies or whole workforce	Generalization within population of survey	Less prone to nonresponse bias	Identifying appropriate comparator population	Selection bias restricts generalizability, especially if particular occupational groups do not attend

CKD, chronic kidney disease; ESRD, end-stage renal disease.

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i.e. in these cases the population that attended the respective clinical service. In the context of CKD there is also the issue that diagnosis is often based on blood and urine tests which the treating clinician must actively order, and there may be reasons why certain groups of people are more/less often tested. For example, a particular group of patients may have differing access to care, e.g. because of lack of insurance or because they are too unwell to attend routine appointments. Furthermore, a patient may receive a kidney function test as the clinician worries about the potential of AKI as the patient is acutely unwell, when a kidney function test may not otherwise be done, a situation that would lead to an underestimate of kidney function in the tested population. Therefore, surveillance for CKD using hospital or primary care records should use results from steady state routine testing, i.e. when the patient was not acutely unwell. Furthermore, any changes in prevalence or incidence over time may be driven by differences in the way people were tested and/or managed rather than changes in disease burden. For example, changes in patient pathway may explain apparent changes in prevalence, e.g. a particular group of patients may now be referred to secondary care when they were previously managed elsewhere or vice versa.

Measurement Error

With all approaches based on the testing of renal biomarkers, it is also important to consider the issues surrounding laboratory calibration and external quality assurance which can be the source of substantial measurement error. Compounding the problem with biomarker measurement error is the fact that the various estimating equations for the eGFR have generally been validated in US and European populations and whether the same relationship between serum creatinine (or cystatin C) and kidney function exists in all populations and in other settings remains unclear. For example, although there is a correction factor for African-Americans in both the Modification of Diet in Renal Disease (MDRD) and CKD-Epi eGFR formulae, evidence suggests these correction factors cannot be applied with certainty to Sub-Saharan African populations [29]. Finally, although again less important if examining CKD within a region, when attempting to compare the burden of CKD between different areas it should be recognized that the distribution of healthy kidney function in many populations remains unknown. Therefore, whether the threshold GFR of 60 ml/min/1.73 m^2 as an indicator of future adverse renal (and cardiovascular) outcomes is appropriate in non-European/North American settings is not established, i.e. is there a role for different GFR thresholds for CKD in different populations?

Outputs from Estimates of CKD Burden from Around the World

As discussed above, the population burden of CKD can be estimated using a range of approaches. The corresponding range of estimates will be of more or less valuable depending on the purpose for which the data are sought (provision of basic medical services, RRT planning, etiological insight, or an understanding of secular or regional trends) as well as the access the population has to specific healthcare resources.

RRT Registries

RRT incidence and prevalence are widely reported as part of nephrology society or health service-led registry initiatives and the number of registries capturing these data worldwide is steadily increasing. Most of these registries were initially developed to describe variation in provision and outcomes of dialysis but the same datasets can provide a surrogate for the incidence of treated stage 5 CKD in some populations, specifically in those countries where RRT is freely available.

Although RRT prevalence is a widely cited figure for health service planning and resource calculations, this figure reflects not only CKD burden but is also a function of the survival of those undergoing dialysis or receiving kidney transplantation (a key metric, but one which varies substantially between different regions of the world). Where available, RRT incidence is likely a more useful estimate of the burden of ESRD in a population. However, individuals receiving of conservative care for kidney failure, an increasing number of the elderly in high income countries, and of course those who have no prospect of receiving any kind of RRT, i.e. the majority of the ESRD population in lower-income countries, will inevitably be excluded from such estimates.

Figure 2.1 summarizes reported RRT incidence from a number of international registries. The highest numbers of patients starting RRT per million population are in the Americas (Mexico and the United States) and East Asia (Taiwan, Thailand, and Japan). Importantly although numbers appear to be stabilizing in a number of high-income settings there continue to be dramatic year-on-year increases in numbers starting RRT in middle-income settings such as Mexico and Thailand. These numbers may represent improved ascertainment, true increases in incidence, or both, but of note, Thailand recently introduced an insurance system by which free peritoneal dialysis is made available to those who require it.

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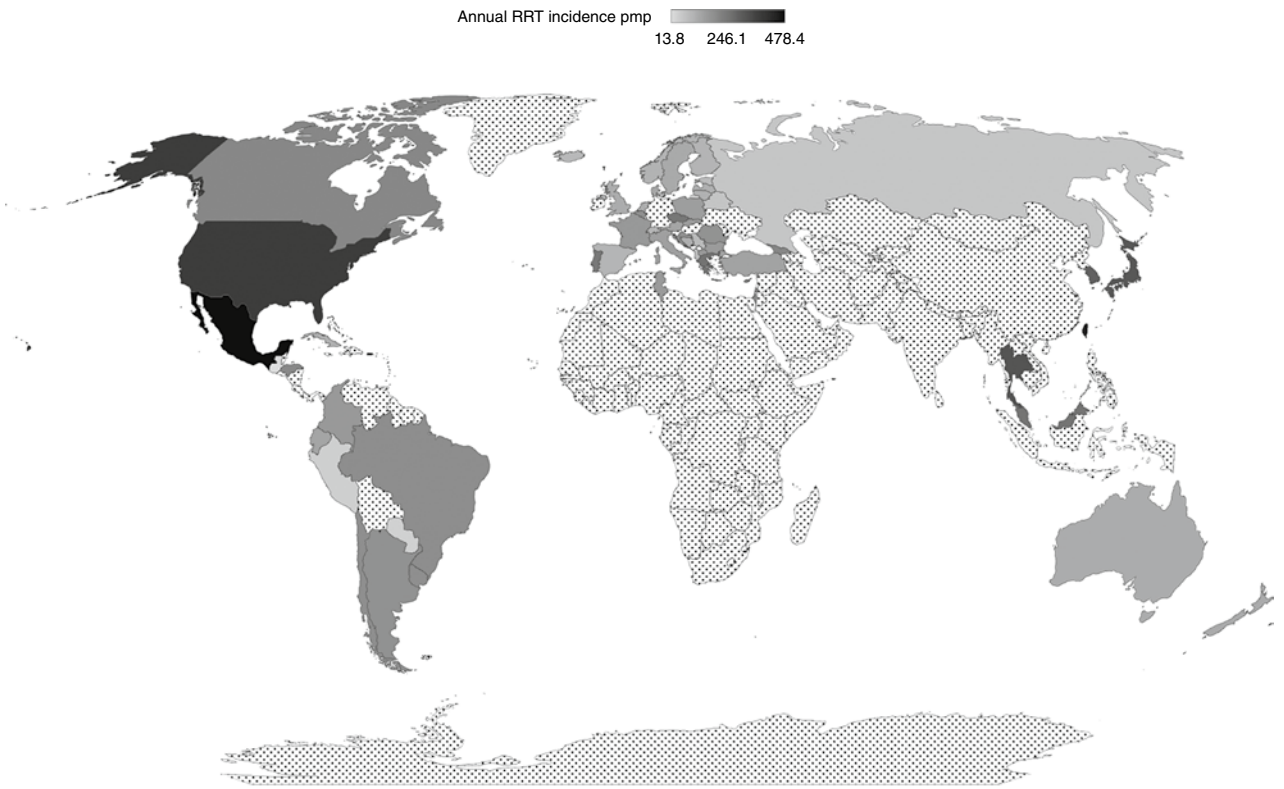

Figure 2.1 Global incidence of renal replacement therapy. Most recent data from publicly available renal registries [30–41], various years. Crude rates per million population. See text for limitations.

Testing of High-Risk Populations

Evidence from high-income countries suggests that most people with CKD can be identified by testing those with risk factors, specifically diabetes, hypertension, those with a family history and older age groups. For example, in the Norwegian population almost 60% of those with an eGFR < 60 ml/min/1.73 m^2 can be captured by testing those with diabetes, hypertension, or a family history of these conditions [17] and this proportion increases to around 90% if everyone in older age groups is also tested.

A number of initiatives aimed at quantifying the burden of CKD have used a similar risk stratification approach to invite individuals for testing (Table 2.3).

Although these approaches are efficient at identification of those with low eGFR and established risk factors such as diabetes, the utility of this approach has not been validated in all populations. For example, those with nonproteinuric CKD living in agricultural communities in low- and middle-income countries would typically not be identified using this type of screening.

Health Systems Data

Health systems that utilize electronic health records have access to a useful source of data on the burden of CKD in the primary care population, for example when used as part of audit and/or quality improvement programs. There is evidence that these programs can in turn lead to improved care processes [44]. Although electronic diagnostic coding of CKD is generally poor in health systems where it is not incentivized (see reference [45] vs. reference [46]), estimates of the burden of CKD can also be obtained by interrogating laboratory records. Coverage is often high, particularly among high-risk groups, because kidney function testing is required for appropriate treatment in those at risk (e.g. hypertension drug management, choice of diabetes drug) and care (many older people receive multiple renal function tests as part of other investigations), hence a high proportion of patients with reduced eGFR are detected. Furthermore, this type of data is useful for demonstrating the chronicity of impaired eGFR or proteinuria. Some examples are shown in Table 2.4.

Population Representative Data

Population-based surveys provide the gold-standard for assessing the prevalence of CKD. Although often challenging to conduct, studies of representative samples with high response rates will provide the best estimates of the burden of disease.

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Table 2.3 Examples of risk-stratification for CKD testing.

Study	Countries	Risk group included	eGFR < 60	Albuminuria	Notes	Reference
KEEP	USA	18 years + First-degree relative with diabetes, hypertension, or kidney disease Personal history of hypertension or diabetes	17%	29% (urinalysis)	Over 90% of those with eGFR < 60 were unaware that they might have abnormal kidney function	[25]
KEEP Mexico	Mexico	18 years + First-degree relative with diabetes, hypertension, or kidney disease Personal history of hypertension or diabetes	Mexico City 7% Jalisco State 10%	Mexico City 19% (ACR > 30 mg/g) Jalisco State 31% (urinalysis)		[42]
Hiperdia Programme	Brazil	Diabetes and hypertension	24.6%	36.6%		[43]

ACR, albumin creatinine ratio; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.

Table 2.4 Studies using electronic health records to estimate CKD burden.

Country	Coverage	Reference
Australia	Melbourne	[47]
Canada	Alberta	[48]
Singapore	Singhealth system	[49]
UK	National (~9% of English and Welsh population)	[46]
	Grampian, Scotland	[50]
United States	Ohio (Cleveland clinic)	[45]
	National (Veterans Affairs Administration)	[51]

CKD, chronic kidney disease.

Population-based surveys have been conducted around the world in attempts to establish the national or regional prevalence of eGFR < 60 ml/min/1.73 m^2, with or without also testing for urinary albumin. Often cross-sectional in nature and nested within epidemiological studies of other noncommunicable diseases, a key issue when interpreting these studies is whether chronicity (i.e. kidney abnormalities present for more than 3 months) has been established. This is important as evidence suggests that between a quarter and one-third of those with a single measure of eGFR < 60 ml/min/1.73 m^2 (albeit those with values only just below the threshold) will have a value above this threshold on retesting [52, 53]. Similarly, variation in the underlying age structure of the population between studies will mean data are not easily comparable across regions without standardization to a reference population.

As discussed above, there are a number of other challenges that arise when comparing these data, including laboratory biomarker quality assurance, validation of GFR estimating equations in different groups as well as a poor understanding of the population distribution of healthy GFR across different regions and ethnicities. Despite these shortcomings this type of cross-sectional survey probably provides the greatest insight into the burden of CKD, particularly in lower-income settings where access to health services, routine laboratory testing, and especially RRT is incomplete. There have recently been international initiatives aimed at conducting simplified population-based studies using standardized protocols with adequately refenced laboratory procedures [54]. It is only using this type of population-representative epidemiological approach that the burden of impaired kidney function (as well as information on specific causes of CKD) can be robustly captured and compared between regions and internationally. Furthermore, these types of study are likely to be key to understanding changes in the burden of kidney disease over time as well as providing the potential to gain insight into previously unappreciated risk-factors for disease.

Examples of population-based studies examining the prevalence of low eGFR (as a surrogate for CKD) are illustrated in Figure 2.2. The highest population prevalence of an eGFR < 60 ml/min/1.73 m^2 has been reported in studies conducted in Cameroon, Iran, Japan, and the countries of Central America. Whether these high rates reflect the age structure of the population, the burden of known CKD risk factors such as diabetes or HIV infection, or reflect specific regional endemic nephropathies is often

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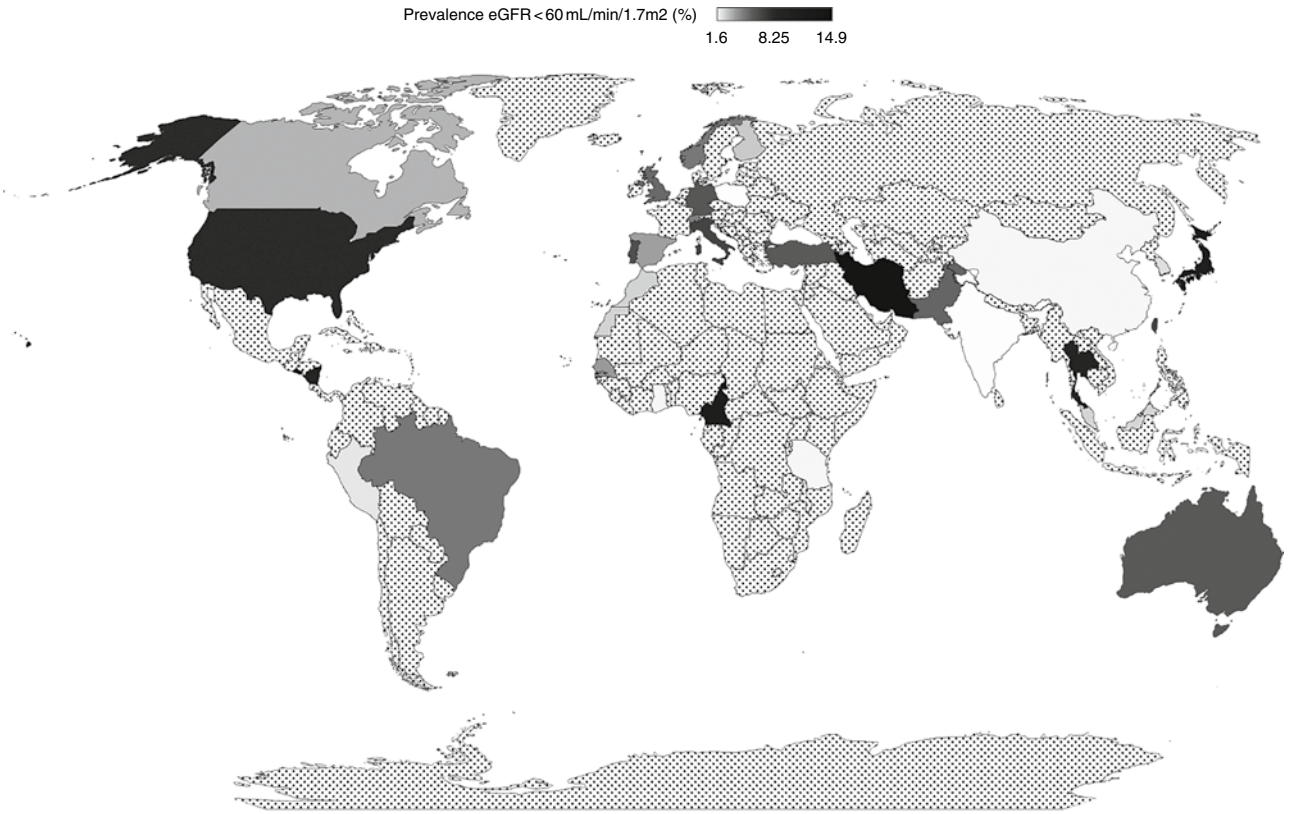

Figure 2.2 Crude prevalence of eGFR < 60 ml/min/1.7 m^2 reported from a range of studies around the world since the year 2000. Includes representative population-based studies aimed at capturing prevalence of CKD across the age range (includes studies that included minimum age as high as 40 years old). eGFR calculated from the CKD-Epi (or MDRD equation where CKD-Epi not provided, and with local correction factors in some cases). Studies only included where external creatinine validation was reported (e.g. IDMS referenced standards) and prevalence standardized to the local age structure where reported. Estimates based on a single measure of eGFR only (see text). *Source:* [26, 52, 55–85].

not fully characterized. However, it is also important to recognize that even country-level figures can often obscure important regional/local differences in CKD prevalence. For example, in Nicaragua age-standardized rates of eGFR < 60 ml/min/1.73 m^2 reach 18% amongst rural males but are less than half that in urban centers in the same region [55].

As might be expected given the issues discussed in this chapter prevalence of impaired kidney function at a population level will not necessarily be reflected in high rates of RRT. However, substantively different RRT rates are reported in settings with similar CKD prevalence even where there is unrestricted access to RRT [56], suggesting there are important modifiable factors in the natural history of disease.

Combined Estimates of CKD Burden: The Global Burden of Disease Project

As none of the above approaches to determining CKD burden can be easily applied to all regions of the world, summary approaches using a composite of all the above approaches may be useful. The Global Burden of Disease project combines data from a huge range of data sources. There are a number of challenges when undertaking this kind of quantification but nonetheless the results are informative. Estimates from this work report a global prevalence of CKD of 3.7% (ranging from 3.4% in low-income regions to 5.3% in high-income regions) [86]. More concerning perhaps is the increase in burden of kidney disease over the last 25 years. Much of this increase originates from aging but increasing rates of diabetes and other causes of CKD are also a substantial contributor in a number of low- and middle-income settings. Globally, CKD now ranks 22nd (from 30th in 1990) of all diseases and accounts for 1.5% (from 0.9% in 1990) of all disability adjusted life years lost.

Summary and Conclusions

No single approach to CKD surveillance will capture all aspects of the burden of CKD comprehensively and data reported from most approaches need to be considered

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alongside any limitations and the health systems context. However, understanding the burden of CKD has an important role in health service planning as well as in quantifying benefits from the introduction of care pathways or interventions by characterizing changes over time. Furthermore, inter-regional comparisons may provide insight into important health inequalities along with the risk-factors and causes of some kidney diseases.

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3

Progression of Chronic Kidney Disease: An Evidence-based Approach to Risk Stratification

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Introduction

Chronic kidney disease (CKD) is associated with significant risks of several adverse outcomes, including progression to kidney failure, cardiovascular events, and mortality [1–4]. Assessment of CKD progression is a chief focus of CKD care and a central target of interventions to prevent the development of kidney failure, an important patient-centered outcome. Kidney failure may be variably defined as initiation of kidney replacement therapy (KRT, including dialysis or kidney transplantation), death attributed to kidney disease, or sustained levels of estimated glomerular filtration rate (eGFR) below a threshold of 15 ml/min/1.73 m^2, which can influence estimates of disease incidence and prevalence [5]. Regardless of definition, there remains significant variability in the risk of progression to kidney failure among patients with CKD. Reliable approaches to risk stratification are important in order to identify high-risk patients who may require specialized care, need closer follow-up or derive greater benefit from certain interventions, and to provide timely psychological or educational preparation and planning for initiation of KRT or a conservative approach to care.

Several prognostic factors for CKD progression have been evaluated in large cohort studies that have characterized associations between clinical and laboratory measurements and risk of kidney failure. Much of this work has been synthesized by the Chronic Kidney Disease Prognosis Consortium (CKD-PC), in a series of patient-level meta-analyses of prognostic factors, usually in relation to eGFR and albuminuria [6]. More recently, prediction model studies have combined prognostic factors to derive and validate multivariable models for kidney failure, which can be used to provide patients and their care providers with individualized estimates of their future risk of kidney failure.

This chapter provides an evidence-based approach to risk stratification for the progression of CKD. A summary of evidence is provided for (i) individual prognostic factors of CKD progression to kidney failure, (ii) validated multivariable clinical risk prediction models for progression to kidney failure, and (iii) the clinical impact of these existing risk prediction models. Where possible, evidence for each prognostic factor is provided from pooled meta-analyses of multiple, high-quality cohort studies, many reported by the CKD-PC. For multivariable risk prediction models, those that have been derived, internally validated, and externally validated in one or more cohorts have been included. Because clinical impact analysis is part of the full evidence base for risk prediction models prior to widespread acceptance and adoption, studies on clinical application and impact are also discussed.

The certainty of evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework for prognosis studies [7]. Because no GRADE criteria are currently available for prediction model studies, their quality has been described according to the extent of external validation and the consistency and generalizability of model performance.

Epidemiology of CKD and Kidney Failure

CKD is common, affecting up to 15% of the population worldwide [8]. In the United States, the reported prevalence of CKD ranges from 7% to 15%, depending whether it is

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defined using eGFR criteria alone or also by the presence of albuminuria [9, 10]. The majority of patients with CKD have earlier stages of disease, with a much lower prevalence of kidney failure reported in the adult population. Among older individuals, in whom multimorbidity can be common, the reported prevalence of CKD is as high as 40% worldwide (approximately 25% in the United States), the majority of whom would be classified as having stage G3a CKD by eGFR criteria (i.e. 45–59 ml/min/1.73 m^2) [11]. The aging population and increased prevalence of cardiovascular disease, diabetes, and other noncommunicable diseases are anticipated to further increase the global burden of CKD and its associated morbidity and mortality [8]. Primary and secondary prevention approaches are desirable so that modifiable risk factors can be addressed to delay development or progression to kidney failure, and to prevent associated complications such as cardiovascular events.

There is substantial variability across the stages of CKD in risk of progression to kidney failure, and a significant amount of research has aimed to characterize the factors that contribute to this risk. The current international CKD staging system [5] categorizes patients according to both eGFR and albuminuria thresholds based on risk relationships, although some have suggested that age- and gender-specific eGFR criteria may be more appropriate, particularly when compared to eGFR alone [12]. Albuminuria was added to the previously accepted eGFR-based classification system following studies demonstrating its association with increased risk of CKD progression and mortality independent of eGFR [13]. Kidney Disease Improving Global Outcomes (KDIGO) has developed a visual "heat map" to identify patients at progressively increased risk for kidney failure at different levels of eGFR and albuminuria (Figure 3.1) [5]. Declining eGFR in combination with increasing albuminuria may better predict progression to kidney failure than either one alone [14]. However, while CKD staging can identify patients at increased risk of progressing to kidney failure, risk for progression on an individual level can vary greatly even within these CKD stages. This suggests that other factors beyond eGFR and albuminuria contribute to the risk of kidney failure, and identification of variables that provide incremental prognostic value could lead to improved risk stratification approaches.

Kidney failure (ESRD)

	ACR <10	ACR 10–29	ACR 30–299	ACR ≥300
eGFR > 105	Ref	Ref	7.8	18
eGFR 90–105	Ref	Ref	11	20
eGFR 75–90	Ref	Ref	3.8	48
eGFR 60–75	Ref	Ref	7.4	67
eGFR 45–60	5.2	22	40	147
eGFR 30–45	56	74	294	763
eGFR 15–30	433	1044	1056	2286

Figure 3.1 Kidney Disease Improving Global Outcomes (KDIGO) CKD Clinical Practice Guideline heat map for risk of kidney failure. eGFR is reported in units of ml/min/1.73 m^2 and ACR in mg/g (multiply by 0.113 to convert to mg/mmol). Values in the cells represent adjusted relative risks. ACR, albumin-to-creatinine ratio; ESRD, end-stage renal disease; eGFR, estimated glomerular filtration rate. *Source:* Levey et al. [13]. © 2011 Elsevier.

Pathophysiology of CKD Progression

Although CKD may result from a wide variety of causes, once it is established, common pathological findings of vascular injury, glomerulosclerosis, and tubulointerstitial fibrosis have been described, regardless of the inciting cause [15]. These maladaptive changes are believed to contribute to a final common pathway of scarring, further nephron loss, and progressive kidney damage that can ultimately lead to kidney failure [16]. Hemodynamic factors, activation of the renin–angiotensin–aldosterone system, and inflammatory responses leading to tubulointerstitial fibrosis are major pathophysiological mechanisms that have been identified in this process.

Both systemic and glomerular hypertension have been identified as common mediators of CKD progression. The afferent and efferent arterioles can moderate glomerular perfusion and pressure independently from systemic blood pressure. However, in the remnant kidney model in rats, reduced nephron mass results in progressive hyperperfusion, glomerular hypertrophy, and glomerulosclerosis [17]. Micropuncture studies suggest that single nephron hyperfiltration in response to renal ablation leads to glomerulosclerosis [18], and animal and human studies suggest that interventions such as renin-angiotensin system inhibitors that decrease glomerular pressure can ameliorate sclerosis, reduce albuminuria, and slow progression of CKD [19].

Tubulointerstitial fibrosis is a second common pathophysiological process associated with CKD progression [20, 21]. While it has been traditionally viewed as a consequence of

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nephron ischemia in CKD [15], more recent mechanistic studies suggest that inflammatory stimuli in response to injury may play an important effect in fibrotic processes in the kidney, moderated via macrophage signaling, cytokines, eicosanoids, and anti-angiogenic factors [22]. These factors may lead to decreased peritubular capillary density and phenotypic transition of interstitial and parenchymal epithelial cells into myofibroblasts, which in turn leads to interstitial fibrosis and glomerulosclerosis, and progressive loss of kidney function [23].

Prognostic Factors for Progression to Kidney Failure

Several commonly ascertained measures have been identified as risk factors or risk modifiers of progression of CKD to kidney failure. The evidence for these laboratory (eGFR and albuminuria), demographic (age, sex, and race), and clinical variables (acute kidney injury, blood pressure, diabetes mellitus, and cardiovascular disease) is reviewed here and summarized in Table 3.1.

eGFR

There is high certainty evidence that reduced eGFR is associated with kidney failure in people with an established diagnosis of CKD, as well as in the general population and those with cardiovascular disease and a high risk of CKD. This finding has been demonstrated when serum creatinine values, standardized to isotope dilution mass spectrometry-traceable methods, are used to estimate glomerular filtration rate (GFR) using either the Modification of Diet in Renal Disease (MDRD) study equation or the CKD Epidemiology Collaboration (CKD-EPI) equation. The first phase of collaborative meta-analysis published by the CKD-PC [4] examined the risk of kidney failure in a total of 21 688 patients from 14 cohorts with CKD, in which the incidence rate of kidney failure varied markedly from 13.6 to 115.3 per 1000 person-years. In adjusted analyses, each decrease in MDRD eGFR by 15 ml/min/1.73 m^2 below a threshold of 45 ml/min/1.73 m^2 was associated with a sixfold increase in hazard of kidney failure. In meta-analysis of cohorts drawn from the general population, with a higher mean eGFR (range 72–144 ml/min/1.73 m^2) and the absolute risk for end-stage kidney disease (ESKD) of 0.31 events per 1000 person-years, the risk of kidney failure was not related to MDRD eGFR at values between 75 and 105 ml/min/1.73 m^2, but was exponentially higher at lower levels of eGFR. At MDRD eGFRs averaging 60, 45, and 15 ml/min/1.73 m^2, and adjusted hazard ratios for kidney failure were 4, 29, and 454, respectively, compared with an eGFR of 95 ml/min/1.73 m^2 [2].

The CKD-EPI equation has been shown to more accurately estimate GFR than the MDRD study equation, especially at higher GFR. A meta-analysis of data from 1.1 million adults from 21 general population, high-risk, and CKD cohorts demonstrated that although the general pattern of the eGFR and kidney failure risk relationship was similar for both equations, eGFR computed by the CKD-EPI equation predicted risk of kidney failure more accurately than the MDRD study equation when eGFR was used for classification into six categories (90, 60–89, 45–59, 30–44, 15–29, and 15 ml/min/1.73 m^2) [24] by both equations. In the general population cohorts, 25.0% of patients were reclassified by the CKD-EPI equation, mostly to a higher eGFR category, with overall reclassification leading to lower risks of kidney failure in patients reclassified into higher eGFR categories and higher risks of kidney failure in patients reclassified into lower eGFR categories. The exception was the MDRD eGFR category of 15–19 ml/min/1.73 m^2, where no significant difference in risk was observed between patients reclassified into the higher eGFR category using CKD-EPI and those not reclassified.

Change in eGFR

A progressive decline in GFR can be viewed as an intermediary on the pathway to kidney failure, and existing evidence suggests with high certainty that a patient's past trajectory of decline in eGFR provides additional prognostic information about the risk of kidney failure, over and above the most recent eGFR available. In a meta-analysis of 232 250 patients from 11 CKD cohorts, where the risk of kidney failure over 2 years of follow-up was 1.4%, a decline in eGFR of 6 ml/min/1.73 m^2 per year over the previous 3 years (i.e. a decline of 18 ml/min/1.73 m^2 versus no decline) was associated with approximately double the adjusted relative risk of kidney failure compared to no decline, whereas a current eGFR of 30 versus 50 ml/min/1.73 m^2 (i.e. a difference of 20 ml/min/1.73 m^2) was associated with 20-fold higher relative risk of kidney failure [33]. These findings thus demonstrate that despite the prognostic value of a change in eGFR, current eGFR is associated more strongly with future risk of kidney failure than the magnitude of past eGFR decline, especially when eGFR falls below 30 ml/min/1.73 m^2.

Albuminuria

Proteinuria can be measured in several ways, including urinary dipstick, albumin-to-creatinine ratio (ACR) or protein-to-creatinine ratio (PCR) on a spot urine sample, or quantification from a 24-hour urine collection. Regardless of the method of assessment, there is high certainty evidence that increasing proteinuria confers a higher risk

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Table 3.1 Summary of findings: individual prognostic factors for kidney failure.

Prognostic factors	Definition of prognostic factor	Evidence source	Summary of findings[a]	Certainty of evidence (GRADE)[b]
eGFR [4]	MDRD eGFR categorized as 30–44, 15–29, and <15 ml/min/1.73 m^2, compared to a reference group with eGFR = 45–74 ml/min/1.73 m^2	CKD prognosis consortium meta-analysis including 14 CKD cohorts, with 21 688 patients	**Absolute risk:** Incidence rate of kidney failure varied between cohorts from 13.6 to 115.3 per 1000 person-years. **Relative risk:** Each decrease in MDRD eGFR by 15 ml/min below a threshold of 45 ml/min/1.73 m^2 was associated with a HR 6.24 (95% CI 4.84–8.05), (I^2 = 87.9%, P < 0.001) eGFR 30–44: HR 2.72 (95% CI 1.29–3.37) eGFR 15–29: HR 10.21 (95% CI 8.36–12.46) eGFR <15: HR 51.48 (95% 31.95–82.97)	**High** ●●●●
CKD-EPI versus MDRD study eGFR [24]	Estimated GFR classified into six categories (90, 60–89, 45–59, 30–44, 15–29, and 15 ml/min/1.73 m^2) by MDRD study and CKD-EPI equations.	CKD prognosis consortium meta-analysis including 1.1 million adults from 21 general population, high-risk, and CKD cohorts	**Absolute risk:** eGFR computed by the CKD-EPI equation predicted risk of ESKD more accurately than the MDRD Study equation; 35% of patients with eGFR 45–59 ml/min/1.73 m^2 by the MDRD study equation reclassified to eGFR of 60–89 ml/min/1.73 m^2 by the CKD-EPI equation and had a lower incidence rate of kidney failure compared with those not reclassified (0.5 vs. 0.8 per 1000-person years). Net reclassification improvement (NRI) significantly favored the CKD-EPI equation for predicting kidney failure; NRI 0.06 (95% CI, 0.02–0.10).	
Change in eGFR [25]	Three-year eGFR slope evaluation	11 CKD cohorts (232 250 patients)	**Absolute risk:** Absolute risk of kidney failure over a mean follow-up of 2 years by eGFR slope; 4.7% for eGFR slope <−5 ml/min/1.73 m^2/year, 1% for eGFR slope ≥−5 to ≤5 ml/min/1.73 m^2/year, 0.1% for eGFR slope ≥5 ml/min/1.73 m^2/year. **Relative risk:** Adjusted hazard ratios of kidney failure, compared to eGFR slope of 0 ml/min/1.73 m^2/year; eGFR slope of −3 ml/min/1.73 m^2/year over preceding 3 years had a HR 1.73 (95% 1.50–2.00), I^2 = 0, eGFR slope of −6 ml/min/1.73 m^2/year over 3 years had a HR 2.28 (95% CI 1.88–2.76), I^2 = 34.3%. No evidence of effect modification of the relative risk of kidney failure associated with eGFR slope according to level of last eGFR (P value for interaction 0.26).	**High** ●●●●
Proteinuria [4]	Proteinuria was categorically defined as follows[c]: ACR (mg/g; multiple by 1.113 to convert to mg/mmol): <30, 30–299, 300–999, and ≥1000 Dipstick proteinuria: −/±, +, ++, +++	Collaborative meta-analysis of 13 CKD cohort studies, including 21 688 patients with follow-up of 1.9–7.5 years	**Absolute risk:** Unadjusted absolute risk kidney failure by ACR category (range of incidence rates per 1000 person-years of follow-up)[d]: ACR <30 mg/g: 2.8–13.8 ACR 30–299 mg/g: 2.8–90.1 ACR 300–999 mg/g: 16.4–141.5 ACR ≥1000 mg/g: 50.2–247.4 Unadjusted absolute risk of kidney failure by dipstick category (incidence rate per 1000 person-years of follow-up)[d]:	**High** ●●●●

(*Continued*)

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Table 3.1 (Continued)

Prognostic factors	Definition of prognostic factor	Evidence source	Summary of findings[a]	Certainty of evidence (GRADE)[b]
			−/±: 5.1 +: 1.2 ++: 44.6 +++: 140.8 **Relative risk:**Adjusted relative risk of kidney failure by ACR category (reference <30 mg/g): ACR 30–299 mg/g: HR 2.87 (95% CI 1.91–4.34) ACR 300–999 mg/g: HR 7.96 (95% CI 6.27–10.09) ACR ≥1000 mg/g: HR 14.61 (95% CI 11.16–19.13) Pooled relative risk for kidney in continuous analyses with an eightfold increase in ACR: HR 2.92 (95% CI 1.96–4.35); I^2 92.2%, $P < 0.001$ Adjusted relative risk of kidney failure by dipstick category (reference −/±)[e]: +: HR 2.92 (2.08–4.10) ++: HR 7.70 (4.52–13.10) +++: HR 15.01 (8.36–26.95)	
Acute kidney injury [26]	Variable definitions of AKI have been used across studies including requirement for acute dialysis, diagnosis codes, and creatinine-based staging	Systematic review and meta-analysis of 13 cohort studies, including 1 472 743 patients with follow-up of 6–75 months	**Absolute risk:** Absolute pooled rate of kidney failure of 8.6 (95% CI 0.63–28.1) events per 100 person-years of follow-up. **Relative risk:** Adjusted relative risk of kidney failure associated with AKI: HR 3.1 (95% CI 1.9–5.0), $I^2 = 98\%$. Relative risk of kidney failure increased in a graded manner with increasing severity of AKI.	**Moderate** ●●●○
Age [27]	Age was categorically defined as follows (in years): 18–54, 55–64, 65–74, ≥75	Individual-level meta-analysis of 46 cohorts, including 2 051 244 patients with a mean follow-up of 5.8 years Separate analyses were conducted on 13 CKD cohorts (38 612 patients)	**Absolute risk:** Absolute risk of kidney failure by age for eGFR of 50 ml/min/1.73 m^2 in CKD cohorts (incidence rates per 1000 person-years of follow-up)[f]: 18–54 years: 38.2 55–64 years: 20.7 65–74 years: 15.1 ≥75 years: 5.7 **Relative risk:** Adjusted relative risk of kidney failure associated with age at an eGFR of 30 ml/min/1.73 m^2 in CKD cohorts (reference eGFR 50 ml/min/1.73 m^2 at age 55–64 years)[d]: 18–54 years: HR 2.85 55–64 years: HR 3.37 65–74 years: HR 3.22 ≥75 years: HR 4.64	**Moderate** ●●●○

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Table 3.1 (Continued)

Prognostic factors	Definition of prognostic factor	Evidence source	Summary of findings[a]	Certainty of evidence (GRADE)[b]
Sex [28]	Male or female	Meta-analysis of 13 CKD cohorts with 38 612 patients, 47% of whom were women	**Absolute risk:** Overall absolute risk of progression to kidney failure was 15.4% among the CKD cohorts. **Relative risk:** Men had higher risks of kidney failure than women, but there was no difference by sex in the relative risk of kidney failure associated with greater albuminuria or reduced eGFR level.	**Moderate** ●●●○
Race [29]	Race was categorized as Asian, White, or Black	Meta-analysis of 45 cohorts, including 1 102 581 patients. Among the 13 CKD cohorts (36 295 patients), the majority were White (83%), and mean follow-up was 6.6–9.2 years	**Absolute risk:** Unadjusted absolute risk of kidney failure by race (incidence rates per 1 000 person-years of follow-up) in all cohorts[f]: Asian 0.3 White 0.8 Black 2.8 **Relative risk:** Adjusted relative risk of kidney failure at eGFR 30 ml/min/1.73 m^2 by race (reference eGFR 50 ml/min/1.73 m^2) in CKD cohorts[d]: Asian 3.09 (95% CI 2.06–4.59) White 2.98 (95% CI 2.48–3.77) Black 2.57 (95% CI 1.3–5.08)	**Moderate** ●●●○
Hypertension [30]	Systolic BP >140 mmHg or diastolic BP > 90 mmHg	13 cohorts of patients with CKD (21 072 without hypertension and 17 088 with hypertension)	**Absolute risk:** Kidney failure occurred in 12.3% without hypertension and 19.5% with hypertension. **Relative risk:** Adjusted hazard ratio for kidney failure estimated at eGFR 30 ml/min/1.73 m^2, by hypertensive status (reference eGFR 50 ml/min/1.73 m^2 in individuals without hypertension)[d]: No hypertension HR 3.20 (95% CI 2.14–4.78) Hypertension HR 3.68 (95% CI 2.87–4.67)	**Moderate** ●●●○
Diabetes [31]	Fasting glucose of ≥7.0 mmol/l, or non-fasting glucose of at least 11.1 mmol/l, or glycated hemoglobin 6.5%, or use of glucose-lowering drugs, or self-reported diabetes	13 CKD cohorts including 38, 612 patients	**Absolute risk:** Unadjusted absolute risk of kidney failure in all cohorts[f]: Total of 5 960 kidney failure events during a mean follow up time of 3.8 years. Absolute risk not stratified by those with versus without diabetes. **Relative risk:** Relative HR = 0.79 (0.56–1.13) averaged across range of eGFR, *P* value 0.19 Relative HR = 1.08 (0.95–1.23) averaged across range of ACR, *P* value 0.22 Adjusted hazard ratio for kidney failure estimated at eGFR 30 ml/min/1.73 m^2, by diabetes status (reference eGFR 50 ml/min/1.73 m^2 in individuals without diabetes)[d]: No diabetes HR 3.26 (2.20–4.74) Diabetes HR 4.93 (3.12–7.70)	**Low** ●●○○

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Table 3.1 (Continued)

Prognostic factors	Definition of prognostic factor	Evidence source	Summary of findings[a]	Certainty of evidence (GRADE)[b]
Cardiovascular disease [32]	Previous diagnosis of myocardial infarction, percutaneous coronary intervention, bypass grafting, heart failure, or stroke	28 cohorts including 185 024 participants from 30 different countries, greater than 18 years of age, with eGFR ≤30 ml/min/1.73 m^2	**Absolute risk:** Unadjusted absolute risk of kidney failure in all cohorts[f]: 22 301 (12.1%) kidney failure overall among the 185 024 patients. Absolute risk not stratified by those with versus without history of CVD. **Relative risk:** HR for history of CVD = 0.91 (0.82–1.02) in the 19 cohorts with outcome information on kidney failure, CVD events, and death. HR for time-varying CVD = 2.28 (2.02–2.57) in the 19 cohorts with outcome information on KRT, CVD events, and death.	**Low** ●●○○

ACR, albumin-to-creatinine ratio; AKI, acute kidney injury; BP, blood pressure; CI, confidence interval; CKD, chronic kidney disease; CKD-EPI, CKD Epidemiology Collaboration; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HR, hazard ratio; KRT, kidney replacement therapy; MDRD, Modification of Diet in Renal Disease.

[a] The majority of the CKD-PC studies defined kidney failure as initiation of kidney replacement therapy (dialysis or kidney transplantation) or death due to kidney disease other than acute kidney injury [4, 24, 25, 27–31], whereas two studies defined kidney failure as initiation of kidney replacement therapy alone [26, 32].

[b] GRADE assessment of the certainty of evidence: High: We are very confident that the true prognosis (probability of future events) lies close to that of the estimate. Moderate: We are moderately confident that the true prognosis (probability of future events) is likely close to that of the estimate, but there is a possibility that it is substantially different. Low: Our confidence in the estimate is limited: the true prognosis (probability of future events) may be substantially different from the estimate. Very low: We have very little confidence in the estimate: the true prognosis (probability of future events) is likely to be substantially different from the estimate.

[c] PCR was not reported in this table as the results were similar to ACR.

[d] Values that were only provided in figures and were approximated using graph digitizing software.

[e] Results are from a single study, Kaiser Permanente Northwest.

[f] CKD-PC includes three cohort types based on source population, general population cohorts, high-risk cohorts selecting subjects at high cardiovascular risk (such as hypertension or diabetes), and CKD cohorts specifically enrolling subjects with CKD. Where not otherwise specified results refer to overall estimates within all three of these cohorts.

of developing kidney failure independently of eGFR and other clinical variables. In a collaborative meta-analysis that included 12 CKD cohorts and 21 321 patients reporting on ESKD outcomes, more severe proteinuria when measured by dipstick, ACR, or PCR was independently associated with an increased risk of kidney failure [4]. Among included studies, the unadjusted incidence rate for kidney failure was as high as 200 events per 1000 person-years in those with greatest degree of albuminuria, compared to rates of less than 10 per 1000 person-years for those with no albuminuria [4]. Similarly, the pooled relative risk of developing kidney failure increased significantly with higher categories of albuminuria, even after adjusting for age, comorbidities, and eGFR. Although there was significant heterogeneity between studies, the point estimates of association did not vary significantly between studies with the exception of one outlier that demonstrated a more strongly positive association between increasing ACR and kidney failure [33].

In the meta-analysis by Astor et al., both lower eGFR and higher albuminuria were independently associated with an increased risk of kidney failure and mortality in CKD cohorts [4]. In one cohort study that stratified by eGFR, patients with heavier albuminuria within each eGFR category had significantly increased adjusted rates of both kidney failure and mortality compared to those with lesser or no albuminuria [34]. In fact, those with heavy albuminuria but without overtly abnormal eGFR appeared to have worse clinical outcomes than those with moderately reduced eGFR and no albuminuria. Increasing severity of albuminuria may predict a more rapid rate of decline in kidney function, regardless of baseline eGFR [35].

These findings highlight the importance of considering the influence of albuminuria in addition to other clinical factors, such as eGFR, when assessing risk of CKD progression, and have contributed to interest in using albuminuria as a surrogate for progression to kidney failure [36, 37]. The most recent international clinical practice guidelines for CKD management acknowledge albuminuria as a valid and important independent predictor of kidney, cardiovascular, and mortality outcomes, resulting in a modification

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of the previous eGFR-based CKD staging system to a risk-based one that considers both severity of eGFR decline and albuminuria [5]. These guidelines refer specifically to use of albuminuria (i.e. ACR) rather than the proteinuria, as albumin is the primary component of urinary protein in most conditions, and the epidemiologic data supporting the association between proteinuria and outcomes is strongest for urinary albumin quantification.

Acute Kidney Injury

Acute kidney injury (AKI) is a potentially avoidable complication that may occur in hospital or the community. There is moderate certainty evidence that patients who have survived AKI have an increased adjusted risk of subsequent progression of CKD and kidney failure compared to those without an episode of AKI [34]. In a large cohort study of nearly one million individuals from Canada, an episode of AKI was associated with higher risk of long-term sustained doubling of serum creatinine or ESKD, with the largest increases in risk seen in individuals with higher eGFR and lesser degrees of proteinuria at baseline [38]. This illustrated that an episode of AKI provides extra prognostic information for progression of CKD in addition to that provided by eGFR and proteinuria. Pathophysiologic processes that are believed to contribute to the transition from acute injury to chronic damage include a failure of differentiation and persistently high signaling activity of regenerating cells in the tubulointerstitium, with inflammation, capillary rarefaction, and fibroblast proliferation ultimately contributing to progression of CKD [39].

In a systematic review and meta-analysis of 13 cohort studies, including over one million patients with follow-up ranging from 6 to 75 months, the pooled incidence of kidney failure was 8.6 events per 100 person-years, and was threefold higher for those with AKI than without AKI. The magnitude of the association between AKI and kidney failure varied substantially between the studies included in this systematic review; however, the definitions for AKI were heterogeneous between studies and all studies reported higher risks among patients with AKI. Furthermore, the risk of kidney failure increased in a graded manner with greater severity of AKI. More recently AKI has also been associated with a later risk of developing CKD even in patients with recovery of kidney function to normal levels [40], and a longer duration of AKI has also been associated with a higher risk of developing CKD [41].

Among patients who have had an episode of AKI, cohort studies have identified several factors that are associated with high risks of developing advanced CKD (eGFR $<30\,ml/min/1.73\,m^2$), including older age, lower baseline eGFR, more severe AKI, and incomplete recovery of kidney function [42, 43]. A multivariable model developed with 9973 participants with AKI and externally validated in a cohort with 2761 participants from Canada included age, sex, AKI stage, prehospitalization serum creatinine level, albuminuria, and discharge serum creatinine in the final risk index [44]. This model achieved a c-statistic of 0.81 and was well calibrated for predicting advanced CKD after hospital discharge. However, the clinical impact of using this model to guide care remains to be evaluated. Whether interventions to prevent AKI or enhance recovery from AKI reduce the risk of progressive CKD and ESKD remains uncertain.

Age

Age does not appear to uniformly influence the risk of developing kidney failure independent of the effect of baseline kidney function and albuminuria. In an individual-level meta-analysis of 46 cohorts and approximately two million patients, the adjusted incidence rate of kidney failure at a given level of eGFR was lowest for persons over age 75 years compared with those in younger age categories (e.g. 9.8 vs. 28.2 per 1000 person-years for ages >75 years and 55–64 years, respectively, at an eGFR of $45\,ml/min/1.73\,m^2$) [27]. However, once eGFR declined to $15\,ml/min/1.73\,m^2$, the adjusted risk of kidney failure was similar across age categories. Among the 13 CKD cohorts in this meta-analysis, similar findings of lower adjusted incidence rates of kidney failure among the oldest age group were reported, although the absolute risk of kidney failure appeared to increase steeply for individuals' ≥75 years of age with an eGFR below $25\,ml/min/1.73\,m^2$ to reach risk estimates comparable to other age groups. Overall, a trend toward lower risk of kidney failure was identified among older individuals, although the absolute and relative risks were not significantly different across age categories.

Kidney function generally declines with advancing age, the significance of which (and the extent to which it is considered pathological) has been debated [45]. In the meta-analysis described above, low eGFR was independently associated with mortality regardless of age, although the relative mortality risk was attenuated with increasing age [27]. Findings from previous studies suggest that elderly individuals are less likely to progress to kidney failure than they are to die from other causes [46], although these risks may vary depending on how kidney failure is defined, an individuals' baseline kidney function, and whether the kidney failure is treated with KRT. In the systematic review by Hallan et al., kidney failure was defined as initiation of dialysis, transplantation, or death as a result of kidney disease. However, this definition may fail to identify those whose who do not start dialysis for kidney failure

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and those who die from a nonkidney-related cause. One large cohort study suggested that whereas the absolute and relative risks of "treated" kidney failure (i.e. receipt of dialysis or kidney transplantation) are higher in younger compared to older people at a given eGFR, the rates of "untreated" kidney failure (progression to eGFR <15 ml/min/1.73 m^2 without renal replacement therapy) were significantly higher in older individuals [47]. This suggests that kidney disease does progress in older adults and that the incidence of kidney failure in this population may be higher than what has been assumed when kidney failure is defined only by receipt of KRT. These findings have implications for clinical practice and decision making for adults of all ages with CKD, including perception and communication of risk, and evaluation of treatment options.

Sex

Although females have a higher prevalence of CKD than males, observational studies from the United Kingdom and North America suggest that females have a lower risk of kidney failure than males [48]. Moderate certainty evidence from a meta-analysis of 13 CKD cohorts from Europe, North and South America, Asia, and Australasia, including 38 612 patients, have confirmed this finding, and also found no differences by sex in the relative risk of kidney failure associated with a greater degree of albuminuria or reduced eGFR [28, 49]. It is not yet clear the extent to which biological differences related to sex versus societal and social norms related to gender influence the higher incidence of KRT in men than in women.

Race

Moderate certainty evidence suggests that a patient's race does not independently influence his or her relative risk of developing kidney failure for a given eGFR, despite variations in baseline risk across racial groups. Pooled data from a meta-analysis of 45 cohorts indicate that the relative risk of kidney failure and mortality increases similarly among the three studied races (i.e. Asian, Black, and White) across a range of eGFR and/or albuminuria, with greatest risk at low eGFR and high albuminuria [29]. The majority of cohorts in this meta-analysis were from the general population, although a similar relationship was observed among the 13 CKD cohorts ($n = 36\,295$, 3% of the study population). For example, compared to a reference eGFR of 50 ml/min/1.73 m^2, Asian, White, and Black patients at an eGFR of 30 ml/min/1.73 m^2 had an approximately 2.5- to 3.5-times increased risk of developing kidney failure after adjusting for measured confounders. This is despite differences in clinical and demographic characteristics and absolute risk of kidney failure among the cohorts and racial groups. It is worth noting that in this study, most Black patients were from US cohorts, most Asian patients were from East Asian cohorts, and few cohorts included multiple racial groups.

The absolute risk of kidney failure appeared to be highest among Black patients in the general population cohorts of this meta-analysis (adjusted incidence rate 2.36 vs. 0.46 in White patients and 0.27 in Asians, per 1000 person-years) [29]. Unadjusted incidence rates in the CKD cohorts were similar. Genetic factors, including apolipoprotein L1 (*APOL1)* gene polymorphisms, contribute in large part to the significantly increased rates of kidney failure among Black patients; *APOL1* mutations, found exclusively in individuals of African descent, have been associated with earlier onset of CKD, increased albuminuria, and a more rapid decline in eGFR [50–52]. Whereas findings from other studies support differences in rates of kidney outcomes across racial groups and nationalities [53–56], race may also predict rate of eGFR decline and development of CKD in persons without known kidney disease. In one US population-based study, Black Americans and Hispanics with normal kidney function experienced more rapid rates of eGFR decline than White Americans and had higher rates of incident CKD [57]. Consistent findings of a relationship between eGFR and renal outcomes regardless of race support the use of internationally adopted practice guidelines that stage CKD according to eGFR and albuminuria without defining specific thresholds for racial groups [5]. However, to address modifiable risk factors and impact care delivery across populations with variable risk, it is important to consider the reasons for such baseline differences, including contributions of socio-cultural, environmental, and genetic influences [58].

Hypertension

As a cause and consequence of CKD [59], hypertension is a target of treatment in CKD, and there is moderate quality evidence that patients with CKD and hypertension have a higher incidence of progression to kidney failure and death. A large cohort study of 300 000 adults within the general population found that there were graded increases in the risk of kidney failure with increasing blood pressure and this relationship was independent of existing kidney disease [60]. These results are further supported by a large US cohort study of 332 544 men that found increasing risk of developing kidney failure with increasing severity of hypertension, with up to a 20 times greater risk among men with stage 4 hypertension in comparison to those with optimal blood pressure [60, 61]. Similarly, an increased risk of kidney failure has also been associated with hypertension in women [62].

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Among patients with CKD, the relationship between hypertension and kidney failure is not uniform and varies based on eGFR and ACR levels. A meta-analysis of 13 CKD cohorts, comprising 21 072 patients with hypertension and 17 088 without hypertension, found an incidence of 19.5% (3327 kidney failure events) among those with hypertension and 12.3% (2597 kidney failure events) in the nonhypertensive patients [30]. Hypertensive patients, characterized by systolic blood pressure ≥140 mmHg and diastolic blood pressure ≥90 mmHg, had a higher risk of kidney failure at an eGFR of 50 ml/min/1.73 m^2 and ACR of 100 mg/g. However, the effect of hypertensive status was attenuated at lower eGFR and higher ACR levels, such that lower eGFR and increasing ACR levels corresponded with increasing risk of developing kidney failure [30] among patients both with and without hypertension. No significant interaction was found when antihypertensive medication use was incorporated into the analysis.

However, there is evidence for a protective effect on progression to kidney failure based on the type of antihypertensive treatment regimen. An individual patient-level meta-analysis of 11 randomized controlled trials (1946 patients) compared antihypertensive treatments with or without angiotensin converting enzyme (ACE) inhibitors and showed that patients with CKD who had proteinuria and were treated with ACE inhibitors were at significantly decreased risk of developing kidney failure (7.4%) in comparison to patients who received other antihypertensive regimens (11.6%) [63].

Taken together, this evidence suggests that hypertension increases the risk of kidney failure in the general population and CKD patients, but the relative prognostic importance of hypertension for progression to kidney failure tends to diminish at later stages of CKD.

Diabetes Mellitus

Diabetes is a common cause of CKD, and individuals with diabetes are at greater risk of kidney failure and mortality [64, 65]. Evidence from a large meta-analysis of over 100 000 patients reported that patients with advanced (i.e. stage G4) CKD and diabetes mellitus had a 30% higher event rate of kidney failure compared to those with advanced (i.e. stage G4) CKD without diabetes [32].

A second meta-analysis including 38 612 patients from 13 CKD cohorts investigated the association of diabetes (defined as fasting glucose of at least 7.0 mmol/l, nonfasting glucose of at least 11.1 mmol/l or HbA1c of at least 6.5%, use of glucose-lowering drugs, or self-reported) with risks of developing kidney failure [31]. These analyses were adjusted for other cardiovascular risk factors, including blood pressure, total cholesterol, body mass index, and history of cardiovascular disease. Findings indicated that diabetic patients had a higher relative risk of kidney failure when the references were set to an eGFR of 50 ml/min/1.73 m^2 and an ACR of 20 mg/g in nondiabetic patients. However, this relationship did not extend across low eGFR and high ACR levels, with no significant difference in the relative risk of kidney failure by diabetes status across the full range of eGFR values (hazard ratio [HR] 0.79, 95% confidence interval [CI] 0.56–1.13, *P* value 0.19) and ACR values (HR 1.08, 95% CI 0.95–1.23, *P* value 0.22). There is low certainty in this evidence due to the variability observed between studies.

While the aforementioned reviews did not specifically compare treated versus untreated diabetes, there is also evidence that patients with poor glycemic control are at greater risk of progression to kidney failure. A Canadian population-based cohort study found that among patients with diabetes and an eGFR of 30–59 ml/min/1.73 m^2, the risk of progression to kidney failure increased with increasing HbA1c [66]. Such patients with an HbA1c between 7% to 9% and higher than 9% had increased relative risks of 22% and 152%, respectively, of developing kidney failure compared to those with an HbA1c level <7%. This risk of kidney failure with increasing HbA1C diminished at eGFR levels of 15–29 ml/min/1.73 m^2.

Overall, individuals with diabetes and CKD have a higher risk of kidney failure in comparison to those without diabetes at normal eGFR and ACR levels, and this risk is heightened among patients with poor glycemic control. However, diabetic status provides less additional prognostic value for kidney failure at lower eGFR and higher ACR levels.

Cardiovascular Disease

Many studies have shown that CKD is associated with the development of cardiovascular disease, and traditional cardiovascular risk factors are also highly prevalent in patients with CKD [3, 67]. Some studies have shown that the risk of cardiovascular events and mortality is a prominent competing event in CKD and may exceed the risk of kidney failure in many patients. A meta-analysis of 28 cohorts across 30 countries included 185 024 patients with advanced CKD (i.e. CKD G4+) and found an overall incidence of 12.1% (22 301 events) for kidney failure requiring KRT [32]. Adjusted meta-analyses suggested no increased risk of kidney failure requiring KRT among those with a history of cardiovascular disease at cohort entry (defined by previous diagnosis of myocardial infarction, percutaneous coronary intervention, bypass grafting, heart failure, or stroke). However, when time-varying cardiovascular events were added to the model, they were significantly associated with

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increased risk of both progression to kidney failure (HR 2.28, 95% CI 2.02–2.57) and mortality (HR 2.87, 95% CI 2.57–3.20). The certainty of this evidence is low due to heterogeneity between the study cohorts and imprecision of pooled estimates.

Risk Prediction Models for Kidney Failure

The best ways to assess patient prognosis use prediction models that combine multiple risk factors to provide estimates of a patient's absolute risk of an outcome. Risk prediction models have been developed and tested in other clinical settings to inform clinical decision making. To be certain that a risk prediction model provides reliable prognostic information, it should undergo validation, ideally in a separate group of patients from those in whom the models were derived, to demonstrate the model's ability to discriminate between patients who will have an event and those who will not. Furthermore, the model should deliver predictions of absolute risk that are well calibrated to observed risks [68]. Three multivariable risk prediction models to predict progression to kidney failure have been developed and externally validated in cohorts with CKD (Table 3.2) [49, 69, 70].

In 2011 Tangri et al. reported the derivation and performance of kidney failure risk equations (KFREs) to estimate 2- and 5-year absolute risks of treated kidney failure, defined by the need for dialysis or a pre-emptive kidney transplant [49]. The models were derived in a cohort of over 3000 patients with CKD (eGFR <60 ml/min/1.73 m^2) cared for by nephrologists in Toronto, Canada, and externally validated in a separate cohort of almost 5000 patients receiving similar care in nephrology clinics in British Columbia, Canada. The most accurate model included eight variables (age, sex, eGFR, albuminuria, serum calcium, serum phosphate, serum bicarbonate, and serum albumin) and achieved a c-statistic of 0.92 in the development cohort and 0.84 in the validation cohort. Prediction model discrimination and calibration was also very good for a simpler, four-variable model including age, sex, eGFR, and albuminuria (Table 3.2). The generalizability of predictions based on the KFREs have since been demonstrated through external validation of the original four- and eight-variable equations in 31 cohorts from North America, Europe, Asia, and Oceania [71], including cohorts with patients not under the care of a nephrologist. The four-variable risk equation maintained very good discrimination and calibration in North American cohorts, although recalibration was required among non-North American cohorts to account for the lower incidence of kidney failure in these geographic regions. These findings provide strong evidence that estimates of the absolute risk of kidney failure can be achieved with a level of accuracy considered helpful for use in clinical decision-making, using demographic and commonly ordered laboratory tests for patients with a broad range of CKD stages.

Shroeder et al. have also developed and externally validated a pragmatic prediction model for the 5-year risk of progression to KRT among patients with stage G3 or G4 CKD [69]. The development and validation cohorts were composed of patients with CKD from two geographically distinct cohorts of patients from a large health maintenance organization in the United States. The final model included eight predictors: age, sex, eGFR, hemoglobin, proteinuria/albuminuria, systolic blood pressure, antihypertensive medication use, and diabetes and its complications. This multivariable model had excellent discrimination, with a c-statistic of 0.95, and maintained very good calibration in the external validation cohort, with the exception of slightly lower observed than predicted risk in the highest-risk quintile. These findings provide further evidence that a combination of demographic, clinical, and laboratory variables that are routinely collected in primary care can provide accurate estimates of the risk of kidney failure for patients across a broad range of stages of CKD.

Multivariable models have also been developed using data from over 260 000 individuals with eGFR <30 ml/min/1.73 m^2 from 30 countries included in the CKD-PC [70]. These models included nine prognostic factors (age, sex, race, eGFR, ACR, systolic blood pressure, smoking status, diabetes mellitus, and history of cardiovascular disease) and were developed to predict 2- and 4-year risks of competing outcomes of CKD, including kidney failure requiring KRT, a nonfatal cardiovascular event, and death. Discrimination of the model for risk of kidney failure at 2 years was very good, and when compared to the original four-variable KFRE developed by Tangri et al. showed similar discrimination (c-statistic 0.81 vs. 0.82), with good calibration when used for risk stratification into risk categories of <20%, 20–40%, and >40% predicted risk of kidney failure. These findings provide evidence that multivariable risk models can also aid with risk stratification for kidney failure in patients with advanced (G4) stage CKD and can be used to provide estimates of this risk in relation to competing risks of other relevant clinical outcomes of cardiovascular events and mortality before or after initiation of KRT.

Since publication of the original KFRE, several studies have examined strategies for model updating, with the addition of new or repeated measures in attempts to improve risk prediction for kidney failure. Tangri et al.

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Table 3.2 Summary of findings: validated multivariable risk prediction models for kidney failure.

Model (author)	Cohort descriptions	Prognostic variables	Predictive performance	Tools for use
Kidney failure risk equations (Tangri et al.) [49]	Derivation cohort of 3 449 patients with CKD stages 3–5 from 2001 to 2008 at Sunnybrook Hospital, University of Toronto Health network, Toronto Canada. 11% developed kidney failure over 5 years Validation cohort of 4 942 patients with CKD stages 3–5 from 2001 to 2008 from the British Columbia CKD Registry. 24% developed kidney failure over 5 years	Eight-variable model; age, sex, eGFR, albuminuria, age, sex, eGFR, albuminuria, serum calcium, serum phosphate, serum bicarbonate, and serum albumin Four-variable model; age, sex, eGFR, albuminuria	Eight-variable model; c-statistic 0.92; (95% CI 0.90–0.93) in the derivation cohort and 0.84 (95% CI, 0.82–0.86) in the validation cohort. Four-variable model; c-statistic 0.91 (95% CI 0.89–0.93) in derivation cohort and 0.85, 0.83, and 0.83 at 1, 3, and 5 years, respectively, in the external validation cohort	A risk calculator is available online at www.kidneyfailurerisk.com, for use with an app for handheld electronic devices at https://qxmd.com/calculate/calculator, and as excel risk calculator provided in the supplementary material of the original publication
Kaiser Permanente risk of renal replacement therapy (RRT) model (Schroeder et al.) [69]	Derivation cohort of 22 460 patients in the Kaiser Permanente Northwest health maintenance organization with stage G3 or G4 CKD from 2002 to 2008. 4.7% developed kidney failure over 5 years Validation cohort of 16 553 patients in Kaiser Permanent Colorado from 2006 to 2008. 2.6% developed kidney failure over 5 years.	Age, sex, eGFR, proteinuria or albuminuria, hemoglobin, diabetes, systolic blood pressure, anti-hypertensive medication, and diabetes with number of complications	Derivation cohort: c-statistic 0.96 (0.95–0.97), $R^2 = 79.7\%$ (78.6–80.8) at 5 years Validation cohort: c-statistic 0.95 (0.94–0.97), $R^2 = 81.2\%$ (79.6–82.6)	An integer-based risk score is available in the original publication
CKD Prognosis Consortium models (Grams et al.) [70]	264 296 patients with eGFR <30 ml/min/1.73 m^2 from 29 cohorts and 30 countries included in the CKD Prognosis Consortium. 4-year risk of kidney failure ranged from <0.5% to 28% across cohorts.	Age, sex, race, eGFR, systolic blood pressure, history of cardiovascular disease, diabetes, albuminuria, smoking history.	c-statistic 0.814 (within cohort range in c-static of 0.680–0.972).	A risk calculator is available online through KDIGO at https://kdigo.org/equation

CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.
Note: In all risk prediction models, kidney failure is defined as initiation of dialysis or kidney transplantation.

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assessed a dynamic risk prediction strategy using time-varying laboratory data in a cohort study of patients with CKD [72]. A latest-available-measurement predictive model with eGFR as a time-dependent predictor incrementally improved risk prediction for kidney failure compared to a static measurement model with only a single eGFR (integrated discrimination improvement 0.73%, 95% CI 0.56–0.90%), providing evidence that incorporating additional eGFR measurements over time can improve risk prediction. There is no good evidence that addition of other biomarkers can significantly improve upon the existing KFREs for predicting risk of kidney failure in CKD populations. In one cohort study of patients with CKD who underwent duplex ultrasonography testing, adding renal resistive indices did not improve risk prediction for kidney failure beyond the four- and eight-variable KFRE [73] models. In another cohort study of patients with CKD who had undergone a kidney biopsy confirming diabetic nephropathy, the addition of a score based on pathological biopsy features (the Diabetic Nephropathy Classification Score of the Renal Pathology Society) to the KFRE did not significantly improve risk prediction of kidney failure [74].

Clinical Application and Impact of Kidney Failure Risk Prediction Models

Several potential clinical uses for prognostic information on kidney failure risk have been proposed, which may include the use of this information by patients and family members, primary care clinicians, specialists, health system payers and policy makers. However, there is little evidence guiding their application and assessing their impact in the clinical setting. Three studies have reported on patient or provider perspectives and experiences on the potential impact of implementation of kidney failure risk prediction models in clinical care (Table 3.3) [75–77].

Table 3.3 Summary of findings: clinical implementation and impact of risk prediction models for kidney failure.

Study	Design	Population	Objective and model implementation	Findings
Chiu 2015 [75]	Quantitative (surveys)	111 nephrologists across Canada	To determine perspectives on the importance of predicting kidney failure, risk thresholds that would influence CKD treatment plans, and experiences using existing risk prediction tools.	80% of respondents were not satisfied with their current ability to predict kidney failure, cardiovascular outcomes, and death, and most indicated that they would use validated risk scores to predict clinical outcomes. Risk prediction over a 1- to 5-year time frame was felt to be important for clinical decision making, such as guiding referral for arteriovenous fistula creation.
Hingwala 2017 [76]	Quantitative (quasi-experimental)	Patients referred for nephrology assessment in Manitoba, Canada from 1 January 2013 to 31 December 2013	To describe the incorporation of the KFRE in a triage system for general nephrology referrals. Patients with a 5-year kidney failure risk of ≥3% were booked with nephrology either urgently (risk ≥10%) or nonurgently (risk 3–10%); those with a risk of <3% were referred back to their family physician.	34% of referrals were classified as low risk and referred back to their family physician. The median wait time for nephrology consultation improved from 230 days to 58 days post triage.
Smekal 2018 [77]	Qualitative (focus groups, interviews, open-ended survey responses)	Adult patients with non-dialysis CKD and their family members ($n = 12$ across two focus groups), and healthcare providers (nurses, nephrologists [$n = 16$ interviews; $n = 40$ survey respondents]) from a multidisciplinary CKD clinic in Alberta, Canada	To explore perceived benefits and challenges of implementing a KFRE-based approach to determine eligibility for multidisciplinary CKD care.	Perceived challenges to implementing a risk-based CKD care approach included lack of capacity to manage low-risk patients outside of the CKD clinic setting and more fragmented care. Perceived benefits included targeted care for CKD patients at highest risk of progression and improved program efficiency.

CKD, chronic kidney disease; KFRE, Kidney Failure Risk Equation.

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Chiu et al. surveyed 111 Canadian nephrologists about their views on and experiences with CKD risk prediction tools [75]. Approximately 80% were dissatisfied with their current ability to predict risk of kidney failure, cardiovascular events, and death among CKD patients, and the majority indicated that they would use validated risk scores if such tools accurately predicted risk and influenced their management to improve clinical outcomes. Furthermore, this survey was able to characterize nephrologist consensus on risk thresholds at which treatment decisions should be made, such as arteriovenous fistula planning when a patient's 1-year predicted kidney failure risk exceeded 30–50%.

Two studies have evaluated the impact of the KFRE in clinical nephrology practice, including in the triage of nephrology CKD referrals [76] and determining eligibility for multidisciplinary CKD clinic care [77]. Hingwala et al. applied a KFRE-based threshold of 3% kidney failure risk over 5 years to triage referrals to specialist nephrology assessment. Approximately one-third of referrals were considered low risk and consequently were referred back to their family doctor with CKD care recommendations provided in a standard "low risk letter." In the post-triage period, the median wait time for nephrology assessment decreased from 230 to 58 days, suggesting that this approach may help improve access to nephrology care for patients at highest risk of progression to kidney failure. Smekal et al. sought the perspectives of patients with CKD, their families, and nephrology healthcare providers on the use of the KFRE to determine patient eligibility for multidisciplinary CKD clinic care (2-year kidney failure risk ≥10%) or general nephrology care (2-year kidney failure risk <10%). In focus groups, interviews, and open-ended survey responses, participants expressed concern about the lack of capacity to manage lower risk CKD patients in the community and loss of services for patients previously followed in the multidisciplinary setting. However, they also recognized the potential efficiency gains and focused allocation of resources in providing targeted CKD care for those at highest risk of kidney failure.

These studies have primarily examined perceptions and experiences surrounding implementation of the KFRE to inform risk-informed nephrology care in the Canadian context. However, the broader clinical impact of using risk prediction models in practice remains uncertain. Although the use of kidney failure risk estimates have been proposed to inform several clinical decisions in CKD management [78], successful strategies for their implementation in clinical practice, utility in clinical decision making, and subsequent impact on patient-, provider-, and system-level outcomes [79, 80] has yet to be comprehensively evaluated. Such data will contribute to the generation of an important evidence base for the effectiveness of kidney failure risk prediction models in the care of people with CKD.

Conclusions

High-quality evidence has established substantial variability in the risk of progression of CKD, and that demographic, clinical, and laboratory variables can provide independent prognostic value for the prediction of kidney failure. eGFR and albuminuria are well characterized, strong risk factors for progression of CKD to kidney failure, with high certainty evidence supporting the use of these variables in combination to assess CKD prognosis. Validated multivariable models that incorporate these and other readily available demographic and clinical risk factors are now available for use as kidney failure risk stratification tools in clinical practice (Figure 3.2). Whether implementation of these risk prediction models in clinical care improves patient outcomes and experiences in CKD care remains uncertain, and further research in the area of clinical application and impact is needed.

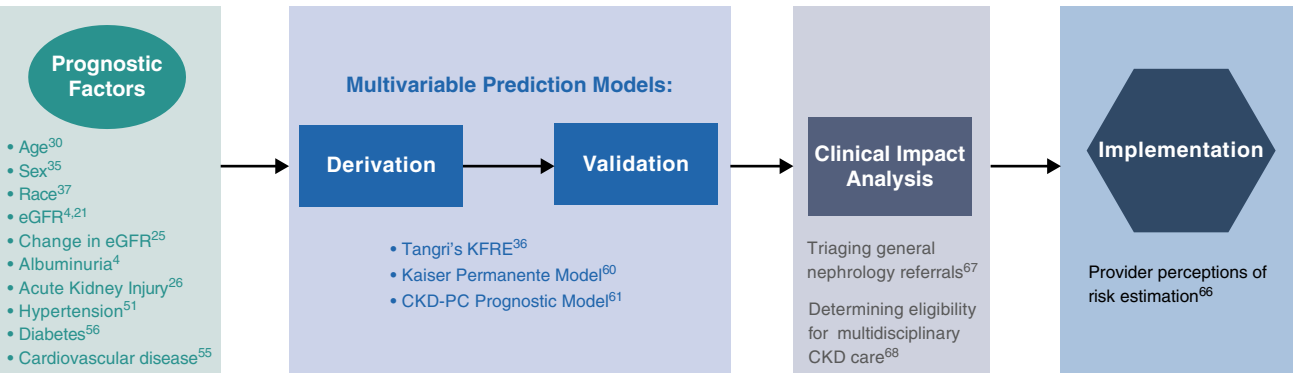

Figure 3.2 Phases in evidence generation to establish risk prediction models for CKD progression in clinical practice. CKD, chronic kidney disease; CKD-PC, Chronic Kidney Disease Prognosis Consortium; eGFR, estimated glomerular filtration rate; KFRE, kidney failure risk equation.

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List of Abbreviations

ACR	albumin-to-creatinine ratio
AKI	acute kidney injury
BP	blood pressure
CI	confidence interval
CKD	chronic kidney disease
CKD-EPI	CKD Epidemiology Collaboration
CKD-PC	Chronic Kidney Disease Prognosis Consortium
eGFR	estimated glomerular filtration rate
ESKD	end-stage kidney disease
GFR	glomerular filtration rate
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HbA1C	hemoglobin A1C
HR	hazard ratio
KFRE	kidney failure risk equation(s)
KRT	kidney replacement therapy
MDRD	Modification of Diet in Renal Disease
PCR	protein-to-creatinine ratio
U.S.	United States

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4

Screening for Chronic Kidney Disease

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An ounce of prevention is worth a pound of cure.
Benjamin Franklin

Introduction

Screening is performed to differentiate healthy people from those in the early stages of disease who are not experiencing symptoms or exhibiting signs of illness. This might be justified when effective early interventions are available that lead to better outcomes, for example screening for motor neuron disease would do more harm than good, given the lack of effective interventions and risk of overdiagnosis, false-positive results, and associated anxiety [1]. This chapter aims to discuss the utility of a screening program for chronic kidney disease (CKD) with regard to associated outcomes and costs.

CKD is highly prevalent in many countries and access to treatment is often limited [2, 3]. CKD tends to be an asymptomatic condition that goes undetected until its later stages when most kidney function has been lost [4]. The asymptomatic nature of kidney disease is one of the main reasons why several patients in developing countries often present late for kidney care when dialysis is urgently needed [5]. Late presentation, which is associated with increased mortality, [6] may be due to late referral; however, a lack of access to healthcare plays a major role in many low-income countries. Screening for CKD and early detection to slow disease progression is thus important in these settings, given the high costs associated with treatment. The findings of one study that assessed the cost utility of one-off, point-of-care screening and treatment for CKD among a rural adult Canadian indigenous population revealed an incremental cost-effectiveness ratio (ICER) of $23 700 per quality-adjusted life-year (QALY) compared to usual care [7]. Findings from a systematic review show the cost-effectiveness ratios for proteinuria screening to be $14 063–$160 018 QALY for the general population, $5298–$54 943 QALY for diabetics, and $23 028–$73 939 QALY for hypertensives [8]. However, the cost-benefit ratios of screening have not been adequately studied in developing countries where such assessments are largely needed.

Who Should be Screened for CKD?

Most countries do not have a coordinated approach to CKD screening, leading to so-called "opportunistic screening." Several researchers have used World Kidney Day as a platform to increase awareness of the importance of CKD screening [9–12]. Because screening techniques are not standardized, data on CKD prevalence often are unreliable, even within a single country or region [10, 13]. Even in countries with national programs for early detection of CKD, treatment plans often are unclear and access to healthcare resources may be limited [14]. Large-scale, population-based screening programs should include follow-up protocols and successful care referrals for individuals who test positive to ensure appropriate diagnosis, treatment, and counseling.

A major problem with screening for CKD revolves around who to screen: the general population or only at-risk populations such as those with diabetes, hypertension, family history of CKD, and other patient groups at

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increased risk for CKD, such as those with HIV. This conundrum has generated much debate [15]. Those in favor of general population screening argue that early identification is clinically and scientifically relevant to reduce the burden of CKD [16, 17], while others use the same argument to support screening among at-risk populations only [4, 8, 18–21]. In a population-based study of dipstick screening, Boulware et al. [22] reported an unfavorable ICER for screening individuals with neither hypertension nor diabetes ($282 818 QALY), but more favorable ratios for screening individuals age 60 and older ($53 372 QALY) and those with hypertension ($18 621 QALY). The authors concluded that routine proteinuria screening is only cost-effective for high-risk populations or when performed very infrequently (i.e. every 10 years) [22]. Those supporting targeted screening even suggest that harms may be associated with mass screening due to false-positive results and unnecessary testing and treatment. Overall, there is insufficient evidence that providing early treatment for patients without risk factors who are identified via screening yields benefits [19]. The American College of Physicians (ACP) recommends against screening for asymptomatic adults without risk factors for CKD, as well as adults who are receiving renin-angiotensin-aldosterone system (RAAS) blockade therapy due to low-quality evidence [23]. Due to insufficient evidence, Kidney Disease – Improving Global Outcomes (KDIGO) did not comment on the benefit of screening for early detection of disease versus the harm of "disease labeling" [24]. As one analysis suggested, screening for CKD may be cost-effective for at-risk patients (i.e. individuals with diabetes and hypertension) and populations with higher incidences of CKD and rapid rates of progression (e.g. HIV-positive patients and relatives of CKD patients) [8, 25].

Methods of CKD Screening and Characteristics of Screening Tests

Ideally, we would like to have a test with very high sensitivity and specificity. However, there is usually a trade off between these two properties of the test. Imagine we want to decide on a cut-off value for estimated glomerular filtration rate (eGFR) to define CKD. The lower the cut-off value, the lower the likelihood of mislabeling a healthy person with CKD, but the higher the likelihood of missing some patients with CKD [26]. Any screening program is associated with costs and potential harms (i.e. false-positive results causing unnecessary anxiety, overdiagnosis, and overtreatment). As the frequency of screening increases the marginal benefit will plateau, and cost and harm will increase disproportionately. Therefore, it is important to choose the right frequency for any screening program [27].

A successful detection method is a test with high validity (i.e. specificity and sensitivity). Such a test should also be highly reliable (i.e. consistently yield the same results when repeated under the same conditions) [28]. Albuminuria is an early and sensitive marker of CKD, whether it is estimated via a 24-hour measurement (gold standard) or dipstick assessment of spot urine. Screening for CKD relies on quick and simple methods to assess kidney function, such as testing urine for protein (albumin) and/or measuring serum creatinine. Although a CKD diagnosis is confirmed based on two abnormal results with a repeat test conducted after a 3-month period [29], for the purpose of screening and early disease detection, one abnormal result is considered a positive test. The CKD prevalence rates reported from screening tests thus depend on the assessment methods utilized, with a potential to under-report or over-report identified cases of CKD [16, 30, 31]. For instance, in a large study in Japan, Uchida et al. [32] showed that a significant proportion of CKD might be under-reported if only dipstick proteinuria is used to assess kidney function, and strongly recommended that both urinalysis and serum creatinine measurement be used in CKD screening. Among 538 846 people, 14.4% had an eGFR below 60 ml/min/1.73 m^2, 5.2% had proteinuria, and 18.1% had CKD, 71.4% of whom had nonproteinuric CKD (47.9% had diabetes mellitus and 66.8% had hypertension). In contrast, a single assessment of serum creatinine level in the third National Health and Nutrition Examination Survey (NHANES III) was reported as misleading due to age, gender, and ethnic variability [33].

Existing CKD Early Detection and Prevention Programs

CKD diagnosis requires detecting persistent structural (albuminuria) or functional (low eGFR) abnormalities of the kidney through laboratory measurements [29]. Collectively, the factors described above make CKD well-suited for population-based screening for early detection and treatment. Wilson and Jungner's first screening principle is the importance of the condition based on its prevalence [34]. Therefore, in this section we examine CKD prevalence data and summarize relevant population-based studies of CKD epidemiology in various parts of the world, and report on recent findings that reveal national capacities for CKD screening and detection with the following objectives:

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- To perform a review of the literature of the population-based epidemiology of CKD.
- To describe such studies in terms of design, scope, population, CKD outcomes, and relevant findings.
- To identify areas for further work.

We conducted an extensive literature review by performing a broad and intensive search for population-based studies of CKD published between 2000 and 2018. We searched several databases (i.e. PubMed, Cinahl, Embase, and Cochrane) using the following keywords: population-based, community, screening, chronic kidney disease, CKD, chronic kidney failure, CKF, end-stage renal disease, ESRD, end-stage kidney disease, ESKD, early detection, prevention, management, risk factors, epidemiology, albuminuria, microalbuminuria, and proteinuria. Only studies that examined CKD and/or albuminuria in a community setting and were published in English were retrieved. To be included, a study had to:

- include a measure of prevalence for CKD and/or albuminuria in a general population
- be based on data collected from adults aged 18 years and older who were recruited from a community-based population sample
- present sufficient detailed methodology and results, as well as ethical approval from the relevant authorities
- be the original and/or most recent publication if multiple studies based on data from the same population exist

To inform efforts for the prevention, detection, and treatment of CKD, it is vital to have high-quality evidence that yields accurate estimates of the disease burden in the population. The most recent systematic review and meta-analysis estimate the global prevalence (44 countries) of CKD to be 13.4% (95% confidence interval [CI] 11.7–15.1%) [35]. Another systematic review and meta-analysis estimates worldwide CKD prevalence to be 10.4% among men (95% CI 9.3–11.9%) and 11.8% among women (95% CI 11.2–12.6%) [36]. These estimates of global CKD burden in the low double-digits were calculated by combining CKD prevalence data published in the literature. There are several methods to obtain population-level epidemiological data on CKD burden, and each has its benefits and drawbacks. The most commonly used are health examination surveys [37]. When coupled with a representative random sample of the national population, these cross-sectional studies can provide insights into the true prevalence of disease and associated risk factors. Moreover, periodic health examination surveys can be used as surveillance tools to monitor disease trends over time. For example, the NHANES, one of the earliest attempts to quantify CKD burden since the introduction of the CKD staging system, has been instrumental in estimating the scale of CKD prevalence in the United States at 13.1% (95% CI 12.0–14.1%) [37]. If well executed, surveys can provide precise data for estimating CKD prevalence. However, they can be associated with limitations related to (i) cross-sectional data collection, which typically entails a single measurement of kidney function instead of repeat testing to establish CKD diagnosis, (ii) the vast financial and human resources required to perform large scale surveys [38], and/or (iii) the methods used to estimate CKD, such as eGFR equations, calibrations, and standardized assays of serum creatinine and albuminuria [39].

Another approach to quantifying CKD burden is to analyze data stored in administrative databases, which often hold records on a large number of individuals that cannot easily be surveyed. These databases often can be repurposed to provide information on CKD burden in the population. For instance, Go and colleagues used data from the Kaiser Permanente renal registry, a sizeable health plan laboratory database in the United States, to estimate the morbidity (cardiovascular events, hospitalization) and mortality associated with CKD [40]. They reported an inverse and graded relationship between a decrease in kidney function and increased risk of death, cardiovascular events, and hospitalization using large population data [40]. This technique has the advantage of obtaining data on a large segment of the population over long periods of time while requiring relatively fewer resources than prospective studies. However, some known disadvantages of this approach are (i) the accuracy of the data, since they typically are collected for purposes other than research, (ii) the representativeness of the target population, because most data in administrative databases are from people with access to healthcare, making generalizability to the whole population challenging, (iii) the lack of well-established health systems that collect data using rigorous methods in many parts of the world, and (iv) the observational nature of these study designs and the potential for biases. Of note, data obtained from surveys can be stored and later linked to other databases or analyzed in retrospective studies to answer different research questions.

The Global Burden of Disease (GBD) studies have revealed additional insights about the burden of CKD. The GBD studies are systematic, scientific efforts using Bayesian inferences and sophisticated statistical modeling to quantify the burden of all major diseases, including CKD [41, 42]. The GBD studies involve more than 3000 collaborators and cover more than 195 countries from 1990 to date. In the GBD studies, CKD's ranking among the hierarchical causes of disability-adjusted life years (DALYs) rose from

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30 to 22 between 1990 and 2016 [43]. In addition, the GBD studies predicted an estimated 28.8% increase in CKD prevalence from 2006 to 2016; importantly, more than half of the increase was attributed to diabetes (+30.1%) and hypertension (+34.7%) [44]. Although GBD studies are currently at the forefront of global efforts to estimate disease burden, they have several limitations, including coding practices, sampling measurement, and case definition errors involved in obtaining and merging this voluminous data from a wide array of sources [41, 42]. Finally, prospective registries that collect data for surveillance and monitoring purposes are important sources for estimating CKD burden. Although end-stage kidney disease (ESKD) registries on disease incidence and prevalence are well established in many developing countries, predialysis CKD registries are almost nonexistent. In the Global Kidney Health Atlas (GKHA) survey, only nine out of 125 countries surveyed reported viable CKD registries [45].

National Capacity for CKD Screening

The GKHA project evaluated national capacities to detect CKD in both primary and secondary care settings (Figure 4.1), including several CKD screening-related anthropometric and laboratory measurements that are necessary to identify CKD risk factors or kidney damage. Interestingly, less than half of low-income countries did not have the capacity to routinely test for serum glucose, serum creatinine urinalysis (qualitative and quantitative), and urine portions in primary care settings. Moreover, none of the low-income countries reported the capacity to automatically report eGFR or test for urine proteins in primary care settings. Similarly, lower-middle income countries reported limited capacity to measure HbA1c and serum creatinine with and without eGFR, and to perform urinalysis (qualitative and quantitative) and measure urine proteins. While less than half of upper-middle income countries had these capacities, the majority of high-income countries reported the availability of these services (Figure 4.1). As expected, CKD-related health services were more available in secondary care settings; however, capacities for automated eGFR reporting and proteinuria assessment were limited compared to the other services, especially in low income countries.

CKD Testing for High-risk Populations

The GKHA evaluated routine testing for CKD among several high-risk populations (Figure 4.2). Across countries in all income groups, CKD testing was almost universal for patients with hypertension and diabetes (94–100%), but minimal for high-risk ethnic populations (<30%). More than 50% of countries tested for CKD in patients with cardiovascular disease who were taking chronic nephrotoxic medications and with a family history of CKD. Elderly populations (age ≥65 years) also were tested for CKD in more than half of the countries in the high and upper-middle income groups, but not in the lower-middle (47%) and low (41%) income groups. Overall, CKD testing rates followed the economic development classification, with the highest rates in higher income countries and lowest rates in low-income countries (Figure 4.2).

CKD Detection Program

The GKHA also evaluated the presence of an active CKD detection program based on national policies and/or guidelines. Overall, less than a third of countries reported having a CKD detection program. Most of the programs were in high-income countries (32%), followed by upper-middle (27%) and lower-middle (22%) income countries. Among the responding low-income countries, only one reported an active CKD detection program (Figure 4.3). The majority of countries with CKD detection programs implemented them through active screening during routine health encounters (68%) or through specific screening processes (57%), while 54% reported a reactive approach in their program implementation (Figure 4.3). These findings indicate that there is no single program implementation approach. Moreover, many countries reported more than a single method in their program implementation.

From what has been presented so far, it can be inferred that many studies have been performed worldwide on the prevalence of CKD at both the national and community levels. Many of these studies are based on the initial observation by the NHANES III that up to 11% of the US population may have CKD. Prevalence of albuminuria/proteinuria in the results ranges from 0.6% to 29.7% in general population studies, and from 2.7% to 45.4% in studies of high-risk individuals. Overall, there is a graded effect in terms of the number and size of the studies observed, from high-income countries to low-income countries. These significant variations may undermine developing countries' abilities to develop screening programs tailored to their contexts. Recent findings from the GKHA that many countries have insufficient capacity for detecting and monitoring CKD in both primary and secondary care settings is concerning. Any discussion of CKD screening programs implies resource availability and testing capabilities. Currently, the two pillars of CKD detection are estimated GFR from serum creatinine and urine proteins, and capacities to perform these measurements are significantly limited in many parts of the world.

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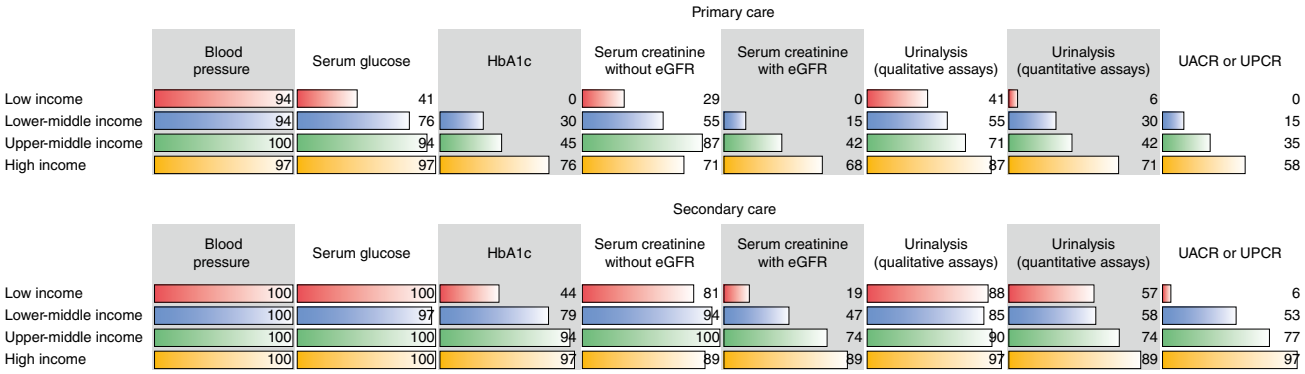

Figure 4.1 Capacity for identification and management of chronic kidney disease in primary and secondary care settings, by World Bank income group. HbA1C, glycated hemoglobin; eGFR, estimated glomerular filtration rate; UACR, urine albumin-creatinine ratio; UPCR, urine protein-creatinine ratio. *Source:* Data sourced from [46].

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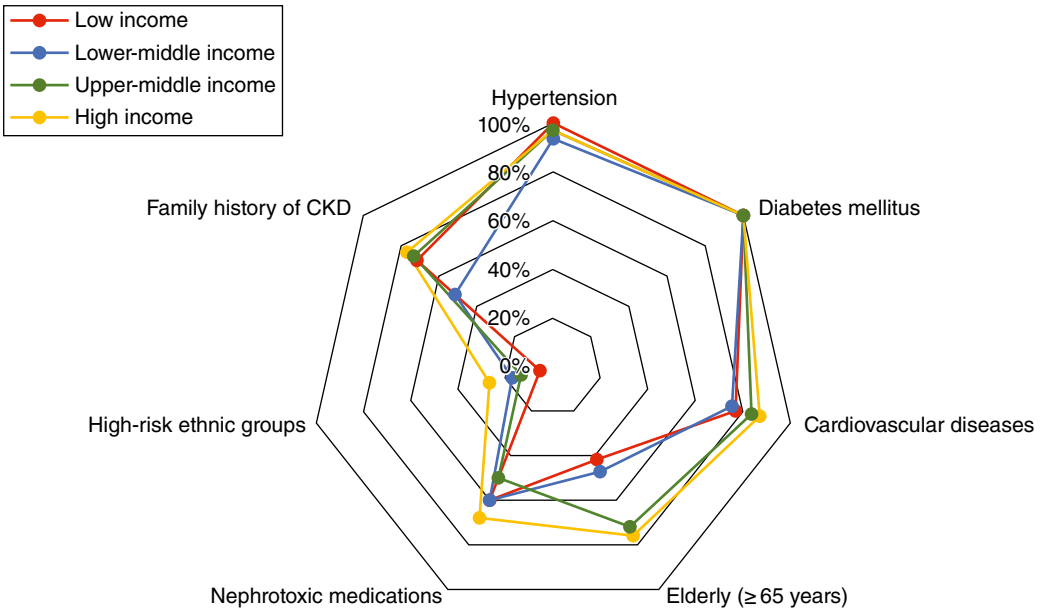

Figure 4.2 Chronic kidney disease testing for high-risk populations, by World Bank income group. CKD, chronic kidney disease. *Source:* Data sourced from [46].

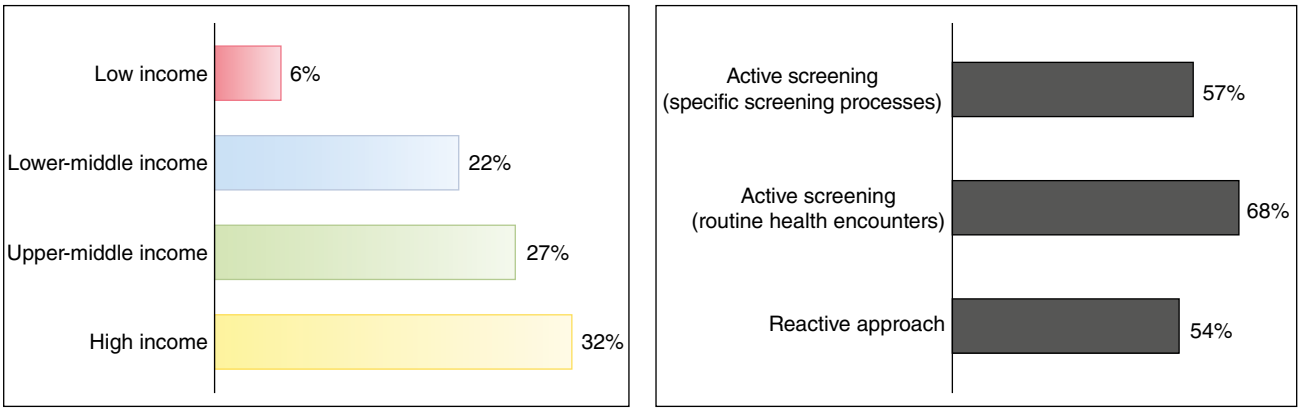

Figure 4.3 Existence of CKD detection programs, by World Bank income group and implementation method. *Source:* Data sourced from [46].

Review of Current Guideline Recommendations for CKD Screening

In 2012, the US Preventive Services Task Force (USPSTF) reviewed evidence related to screening for CKD in asymptomatic adults and concluded that it is insufficient to assess the balance of benefits and harms of routine testing. Thus, they did not provide any recommendations in their report, even for people with diabetes and hypertension [47]. Likewise, the ACP did not find any randomized control trials evaluating the benefits or harms of screening for CKD stages 1–3 among the general population. They pointed out potential harms of universal screening, including disease labeling, adverse effects of testing and treatment, and financial consequences. Thus, they recommended against screening for CKD in asymptomatic adults without risk factors for CKD (grade: weak recommendation, low-quality evidence). They also recommended against testing for proteinuria in adults with or without diabetes who are currently taking an angiotensin-converting enzyme inhibitor (ACEi) or an angiotensin II–receptor blocker (grade: weak recommendation, low-quality evidence). The ACP also found the current evidence insufficient to evaluate the benefits and harms of screening for CKD in asymptomatic adults with CKD risk factors [23]. These recommendations were endorsed by the American Academy of Family Physicians

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(AAFP) in a guideline statement published in 2014 [48]. In the UK, the National Institute of Health and Care Excellence (NICE) made several recommendations regarding CKD screening for at-risk populations [49]. NICE did not make any explicit recommendation for asymptomatic people without known risk factors for CKD, and strongly recommended against using age, gender, ethnicity, obesity in the absence of a metabolic syndrome, diabetes, or hypertension as risk factors. For people with risk factors for CKD, they recommended offering CKD screening tests, and for patients with nephrotoxic drug prescriptions, they strongly suggested annual screening for CKD.

Although the American Society of Nephrology does not have a guideline, it issued a press release in response to the ACP guidelines in which they strongly suggested screening for CKD among general populations, regardless of risk factors [50]. In 2013, KDIGO published one of the most comprehensive guideline recommendations for management of CKD; however, these guidelines do not explicitly include screening recommendations [29]. In 2002, the National Kidney Foundation (NKF) and the Kidney Disease Outcome Quality Initiative (KDOQI) had recommended screening at-risk individuals for CKD [51]. In a 2014 commentary on the 2012 KDIGO guidelines, they highlighted KDIGO's lack of specific recommendations for CKD screening and endorsed their previous recommendation to screen individuals at high risk for developing CKD [52]. They disagreed with the ACP's recommendation not to screen patients who take ACEi or angiotensin receptor blocker (ARB) medications.

Other renal organizations around the world have published their own commentaries or recommendations, with a common theme of screening individuals at high risk for CKD. In its commentary on the KDIGO guidelines, the Canadian Society of Nephrology outlined consensus statements. They did not recommend screening individuals for CKD, but recommended that practitioners continue to use case findings as a means to identify patients with CKD in high-risk populations [53]. The Kidney Health Australia – Caring for Australasians with Renal Impairment (KHA-CARI) guidelines strongly recommend screening people at higher risk of CKD due to diabetes, hypertension or established cardiovascular disease (1B), or additional risk factors such as obesity, a history of smoking, Aboriginal and Torres Strait Islander heritage, family history of stage 5 CKD or hereditary kidney disease in a first- or second-degree relative, or severe socioeconomic disadvantage (1D) [54]. Similarly, the UK Renal Association strongly recommends screening patients at higher risk of CKD (1B) [55]. These recommendations are summarized in Table 4.1.

Effectiveness of Screening for CKD in Terms of Costs and Consequences

Given its silent nature and associated negative consequences, early detection and treatment of CKD must be emphasized. One way to achieve these goals is to perform primary screening for CKD using blood or urine tests; however, it is important to understand the cost-effectiveness of doing so prior to adopting such an approach [8, 56–59]. In healthcare settings, decisions typically are made with consideration to benefits, risks, and costs, yet the economic component of any program arguably is the key determinant. Economic analyses are decision tools based on formal quantitative methods to investigate and compare program adoption to the usual care and/or no care while taking into account the costs of diverting resources from competing priorities, otherwise known as opportunity costs. The most widely used economic measurement to compare and evaluate programs with different costs and outcomes is ICER. ICER is the ratio of the difference in costs to the difference in benefits of the program or intervention. Costs typically are represented in monetary terms, while benefits are expressed in clinical terms such as life-years gained (LYG) or lost, or QALYs gained or lost. QALY is a bi-dimensional composite measurement of length of life and quality of life expressed in a single number. ICER is a way to ascertain both the effectiveness and cost of an intervention compared to another, hence the name cost-effectiveness. Additionally, interpreting ICER requires a value judgment to be placed on the opportunity cost of QALY or LYG. Since data on opportunity costs are limited, determining this threshold can be challenging and tends to be based either on historical funding decisions (e.g. $50 000 per QALY from dialysis) or consensus agreements (e.g. $80 000 per QALY).

Several studies have looked into the cost-effectiveness of screening for CKD using eGFR and/or proteinuria [59–70]. These studies (chapters 17, 22,59 and 62–67) are nicely summarized in a recent systematic review on the cost-effectiveness of CKD screening studies from 1992 to 2012 (Table 4.2) [8]. In this section, we use these systematic review studies as a framework to evaluate the cost-effectiveness criteria for CKD screening.

None of the included studies were randomized control trials, and all were based on Markov simulation models. Seven of the studies evaluated proteinuria, one study evaluated eGFR, and another study evaluated both proteinuria and eGFR as CKD screening methods. The comparator to screening was usual care in four studies, no screening in three studies, and both in two studies. As cost-effectiveness modeling assumptions depend on high-quality evidence, all of the included cost-effectiveness studies were based on

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Table 4.1 Screening recommendations by the professional medical and nephrology societies.

Organization	Nature of organization	Date	Population	Recommendation statement	Strength and evidence of recommendation
US Preventive Services Task Force	Government/ Generalist	2012	Asymptomatic adults without diagnosed CKD	No recommendation	Grade I (insufficient evidence): The evidence is insufficient to assess the balance of benefits and harms of routine screening for CKD in asymptomatic adults. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.
American College of Physicians	Generalist	2013	Asymptomatic adults without risk factors for CKD	ACP recommends against screening for chronic kidney disease in asymptomatic adults without risk factors for chronic kidney disease	Grade: Weak recommendation, low-quality evidence
American Academy of Family Physicians	Generalist	2014		Endorsed recommendation made by the American College of Physicians	
National Institute of Health and Care Excellence (NICE), UK	Generalist	2014; updated 2015	People prescribed nephrotoxic drugs	1.1.27 Monitor eGFR at least annually for people prescribed drugs known to be nephrotoxic, such as calcineurin inhibitors (for example, cyclosporin, or tacrolimus), lithium and non-steroidal anti-inflammatory drugs (NSAIDs) (2008, amended 2014)	Strong
			People with risk factors for CKD	1.1.28 Offer testing for CKD using eGFR creatinine and ACR to people with any of the following risk factors: diabetes, hypertension, acute kidney injury, cardiovascular disease (ischemic heart disease, chronic heart failure, peripheral vascular disease, or cerebral vascular disease), structural renal tract disease, recurrent renal calculi or prostatic hypertrophy, and multisystem diseases with potential kidney involvement, e.g. systemic lupus erythematosus, family history of end-stage kidney disease (GFR category G5), or hereditary kidney disease, opportunistic detection of hematuria	Strong
			Asymptomatic adults	1.1.29 Do not use age, gender or ethnicity as risk markers to test people for CKD. In the absence of metabolic syndrome, diabetes, or hypertension, do not use obesity alone as a risk marker to test people for CKD [2008, amended 2014].	Strong

(*Continued*)

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Table 4.1 (Continued)

Organization	Nature of organization	Date	Population	Recommendation statement	Strength and evidence of recommendation
American Society of Nephrology	Renal organization	2013	Asymptomatic adults	Strongly recommends regular screening for kidney disease, regardless of an individual's risk factors	
National Kidney Foundation/Kidney Disease Outcomes Quality Initiative	Renal organization	2002	Individuals at risk for CKD	Guideline 3: Individuals at increased risk of CKD: Some individuals without kidney damage and with normal or elevated GFR are at increased risk for development of CKD. All individuals should be assessed, as part of routine health encounters, to determine whether they are at increased risk of developing chronic kidney disease, based on clinical and sociodemographic factors. Individuals at increased risk of developing CKD should undergo testing for markers of kidney damage and to estimate the level of GFR. Individuals found to have CKD should be evaluated and treated as specified in Guideline 2. Individuals at increased risk but found not to have CKD should be advised to follow a program of risk factor reduction, if appropriate, and undergo repeat periodic evaluation.	Opinion
		2013	Individuals at risk for CKD	The commentary work group endorses the recommendations from the original guideline for screening among individuals at high risk for CKD despite the absence of this specific recommendation in the KDIGO guideline, and as such is in agreement with the recommendation of the ACP to screen asymptomatic adults only if they are at high risk for CKD.	Opinion
Kidney Disease Improving Global Outcomes	Renal organization	2013		Screening of CKD was beyond the scope of the CKD Work Group and no specific recommendations were made.	
Canadian Society of Nephrology	Renal organization	2015	Asymptomatic individuals	No screening	Consensus

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			At risk of CKD	Practitioners should continue to use case findings in keeping with usual clinical practice: in people with new onset or long-standing hypertension or diabetes, people with vascular disease, people who are to undergo major surgery or be exposed to other potential causes of acute kidney injury, people with multisystem or generalized symptoms, people who are being considered for nephrotoxic medications or medications that require dose adjustment for renal function, people with a family history of polycystic kidney disease or hereditary nephritis, and people from First Nations populations or other ethnic groups known to be at increased risk.	Consensus
KHA-CARI Guidelines	Renal organization	2013	Diabetes, hypertension, or established cardiovascular disease.	We recommend that screening for CKD be targeted and performed in individuals at increased risk of developing CKD, including those with diabetes mellitus, hypertension, and established CVD	1B
			Additional risk factors such as: obesity, cigarette smoking; Aboriginal and Torres Strait Islander peoples; family history of stage 5 CKD or hereditary kidney disease in a first- or second-degree relative; and severe socioeconomic disadvantage.	We recommend screening in those with additional CKD risk factors identified in Guideline 2a (obesity, cigarette smoking, Aboriginal and Torres Strait Islander peoples, family history of stage 5 CKD, or hereditary kidney disease in a first- or second- degree relative and severe socioeconomic disadvantage) (1D)	1D
UK Renal Association	Renal organization	2011	At-risk for CKD	Guideline 1.4 – CKD: Detection and monitoring of CKD: We recommend that patients who are at increased risk for developing CKD should be offered screening tests to detect CKD.	1B

CKD, chronic kidney disease; ACP, American College of Physicians; NICE, National Institute of Health and Care Excellence; eGFR, estimated glomerular filtration rate; ACR, albumin to creatinine ratio; KDIGO, Kidney Disease Improving Global Outcomes; KHA-CARI, Kidney Health Australia – Caring for Australasians with Renal Impairment; CVD, cardiovascular disease.

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Table 4.2 CKD cost-effectiveness studies.

Study	Study population	Screening method	Summary measure	Comparator	Perspective	Screening frequency
		Proteinuria-based screening				
Boersma et al. [62]	General Dutch population aged 28–75 years	Microalbuminuria (UAE 30–300 mg/day)	Cost/LYG	No screening	Healthcare payer	One-off
Boulware et al. [22]	US adults aged 50–75 years	Proteinuria (dipstick)	Cost/QALY	Usual care	Societal	Annual
Hoerger et al. [63]	US adults aged 50–90 years	Microalbuminuria (ACR 30–299 mg/g)	Cost/QALY	No screening and usual care	Healthcare payer	1-, 2-, 5-, 10-year intervals
Howard et al. [64]	Hypertensive and diabetic Australian adults aged 50–69 years	Proteinuria (dipstick followed by spot UPCR; 0.20 mg/mg confirmatory test)	Cost/QALY	Usual care	Healthcare payer	Annual
Kessler et al. [65]	Swiss adults aged 50–90 years	Microalbuminuria (ACR 30–299 mg/g)	Cost/QALY	No screening and usual care	Healthcare payer	1-, 2-, 5-, 10-year intervals
Kondo et al. [17]	Japanese adults aged 40–74 years	Proteinuria (dipstick)	Cost/QALY	No screening	Societal	Annual
Palmer et al. [66]	US hypertensive, type 2 diabetics	Microalbuminuria (UAE 20–199 mg/min)	Cost/QALY	No screening	Healthcare payer	Annual
Siegel et al. [67]	US insulin-dependent diabetics (aged 15 years at diagnosis)	Proteinuria (dipstick 300 mg/min)	Cost/LYG	Usual care	Healthcare payer	Biannual
		eGFR-based screening				
Kondo et al. [17]	Japanese adults aged 40–74 years	eGFR (<50 ml/min/1.73 m^2 and hypertension, diabetes, or hyperlipidemia)	Cost/QALY	No screening	Societal	Annual
Manns et al. [59]	Canadian healthcare system	eGFR (<60 ml/min/1.73 m^2)	Cost/QALY	Usual care	Healthcare payer	One-off

ACR, albumin-creatinine ratio; eGFR, estimated glomerular filtration rate; LYG, life-year gained; QALY, quality-adjusted life-year; UAE, urinary albumin excretion; UPCR, urinary protein-creatinine ratio. *Source:* Adapted with permission from Komenda et al. [8].

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data from high-income countries in North America (the United States and Canada), Europe (Netherlands, Switzerland), Asia (Japan), and Australia. The majority of studies took a healthcare perspective while two studies adopted a broader social perspective. Screening frequency varied from annual to biannual, to several year intervals, and some evaluated on–off scenarios. The majority of included studies determined cost ratios by measuring cost to QALYs; however, two studies used cost to LYG as the summary measure (Table 4.2). Proteinuria-based studies yielded a wide range of cost ratios ranging from $14 000 to more than $160 000 per QALY among the general population, from $5000 to more than $50 000 per QALY among people with diabetes, and from $23 000 to more than $70 000 among hypertensive populations (Figure 4.4). In eGFR-based studies, the cost ratio was around $100 000 per QALY for the general population in two studies and $20 000 per QALY for diabetes patients in a single study (Figure 4.4).

Although population-based screening offers potential benefits such as early identification and treatment of affected patients, it also has drawbacks, such as identification of patients with mild disease who may not need additional treatment [59]. Findings show that screening for moderately increased albumin excretion (microalbuminuria), which is a marker of early-stage CKD, is cost-effective for patients with diabetes or hypertension [22, 36, 68]. Early detection, appropriate risk stratification, and subsequent treatment of CKD may delay or prevent many associated complications, with concomitant increase in cost [7, 69].

Mass screening of the general population for CKD is not recommended because it is not cost-effective for low-risk groups [23, 41]. In contrast, targeted screening of high-risk individuals, such as those with diabetes or hypertension or both, is cost-effective [23, 33]. Screening also is a cost-effective strategy for certain high-risk ethnic groups, such as African Americans and indigenous people of Canada, who are at increased risk of kidney failure and its numerous complications [31]. The cost-effectiveness of a screening program for proteinuria among US adults with hypertension and diabetes has been clearly demonstrated in terms of reducing death and slowing the progression of kidney disease by using an ACEi or ARB [59].

Overall, the cost-effectiveness ratio of screening versus the usual care (no screening) is unfavorable for the general population ($282 818 per QALY saved). Just 0.0022 QALYs per person are gained by preventing of one new case of ESKD and seven deaths per one million persons per year. For individuals with hypertension, the cost-effectiveness ratio of screening versus no screening is considered highly favorable ($18 621 per QALY-saved) [22], with 0.03 QALYs per person gained through the prevention of 14 new cases of ESKD and 104 deaths per 1 million persons per year. For persons with diabetes, the cost-effectiveness ratio of screening versus no screening is overwhelmingly positive ($217 per QALY saved), with a gain of 0.10 QALYS per person due to the prevention of approximately 84 new cases of ESKD and 541 deaths per 1 million persons per year [22]. The results of a similar study carried out among members of the Canadian indigenous community demonstrate that screening and treatment for CKD is highly cost-effective, with a cost-effectiveness ratio of $23 700 per QALY saved. The cost-effectiveness ratio of CKD screening is even more profound in the most remote communities accessible only by air travel, at $7790 per QALY saved [7]. Integrating additional benefits of screening and treatment into the existing framework may improve the cost-effectiveness of the given screening intervention [7, 22]. In previous studies,

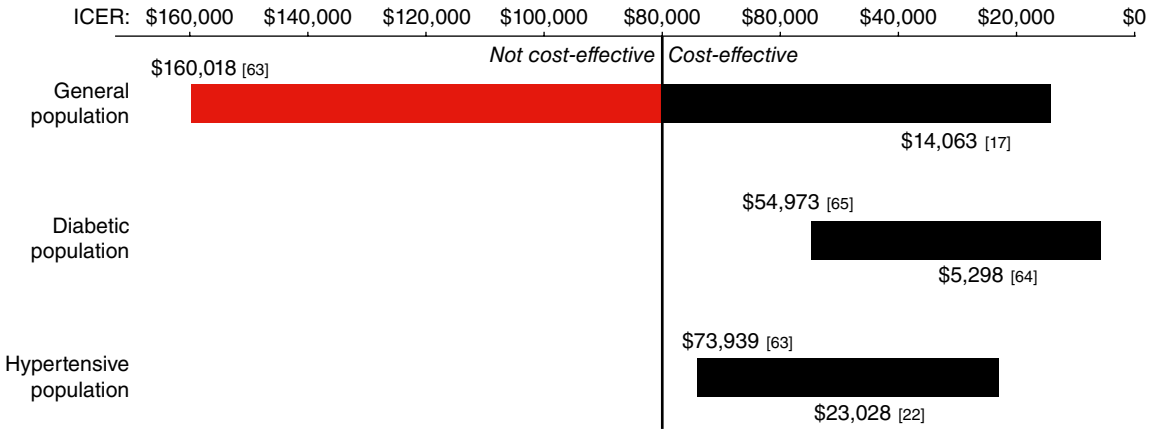

Figure 4.4 Tornado plot comparing reported incremental cost-effectiveness ratios (ICERs) of CKD screening in selected populations.$80 000 ICER selected based on 1–3 times gross domestic product per capita threshold for most G8 (Group of 8) countries. *Source:* Adapted with permission from [8] © 2014 Elsevier.

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researchers have considered the impact of albuminuria screening on the reduction of cardiovascular events and found screening to be cost-effective, even for the general population [62, 70]. Some potential benefits of screening include the reduction of cardiovascular events among patients with diabetes through the use of blood pressure lowering medication, and the potential for increased utilization of statins in newly identified CKD cases [71–73]. In addition, newer therapies such as sodium-glucose cotransporter 2 inhibitors can provide benefits for patients with type 2 diabetes and high cardiovascular risk [74].

Multiple factors could influence the efficacy of these treatment modalities, such as prevailing usage rates for each pharmacotherapy, the underlying prevalence of untreated diabetes in screened communities, and ancillary effects of screening programs such as community education, increased awareness, and lifestyle interventions [7]. Overall, the effectiveness of CKD screening and treatment could be better measured in a cluster randomized trial that can better capture multiple concurrent effects and their influences on patient outcomes [7]. Direct and indirect cost savings associated with screening are primarily achieved through the prevention of new (and expensive) ESKD cases [64]. Years of life saved through the death prevention effects of ACEi and ARB therapies are augmented by the prevention of ESKD cases and their associated high mortality [22, 60]. A lack of cost-effectiveness arises when the prevalence and incidence of proteinuria are very low (leading to few preventable cases of ESKD), and also when the risk of death is very low [64]. Physicians must consider many factors when making decisions regarding early disease detection. Numerous studies [22, 60, 64] have elucidated the key variables that might improve cost-effectiveness, including adherence to ACEi or ARB therapy, the incidence of proteinuria, sensitivity, and specificity of testing, the effectiveness of ACEi or ARB therapies in slowing the progression toward ESKD or preventing death, and decreased frequency of screening [22, 60, 68].

Summary

Screening the general population for early CKD is not cost-effective and therefore is unwarranted. Selective screening should be directed toward high-risk groups (older persons and persons with hypertension and diabetes, and some ethnic groups such as African Americans and indigenous populations of Canada, the United States, and Australia). Adherence to ACEi or ARB pharmacotherapy in preventing death or progression toward ESKD and the frequency of screening play prominent roles in the cost-effectiveness of screening members of the general population.

Decision makers often are pressured to adopt policies that are not necessarily economically sound. However, in a healthcare environment characterized by scarce resources and competing demands, it is essential to consider how to maximize value. Economic evaluations introduce an evidence-based perspective to these decisions. In the case of CKD, the most recent evidence indicates that CKD screening is warranted only for high-risk patients, especially those with diabetes and hypertension, to prevent associated cardiovascular morbidity and mortality. More research is needed to evaluate the armamentarium available for CKD screening and its cost-effectiveness.

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5

Risk Prediction in Chronic Kidney Disease

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Introduction

Chronic kidney disease (CKD) is a major public health issue, with the global prevalence currently estimated to range between 8.7% and 18.4% [1]. CKD is independently associated with an increased risk for end-stage renal disease (ESRD), cardiovascular events, and all-cause mortality, but at the individual level these associations do not necessarily provide prognostic information for providers or patients [2–4]. Accurate risk prediction integrated into clinical practice, based on clinically relevant risk factors, would allow physicians to determine patient-level risk of adverse events at point of care, and in turn stratify patients based on their risk for adverse events [5].

Clinical methods of estimating risk provide assistance to clinicians and patients in shared decision making, ultimately ensuring that patient-centered care is provided [6, 7]. While data-driven decision making is critical to improve patient outcomes, there is no guarantee that accurate estimation of risk translates into improved decision making nor to overall improved outcomes. With the effective use of these risk prediction models, most patients with stage 3 CKD (glomerular filtration rate [GFR] <60 ml/min/1.73 m^2) can be stratified into the low-risk category and have the potential to be treated solely by their primary care provider, allowing for observation and avoidance of premature intensive treatment modalities. Conversely, those at high risk can be referred to nephrology for urgent care [8]. On the same note, models predicting progression toward ESRD can guide decisions about treatments aimed at slowing the progression of kidney disease, assist with dialysis planning and transplantation, and help triage highest-risk referrals to nephrologists [9]. Models that accurately predict cardiovascular disease (CVD) in patients with CKD may help identify patients whose profiles warrant more intensive cardiovascular risk management, such as antiplatelet therapy and lipid-lowering medications. The creation of such clinical decision tools is based on the collection of clinical and demographic variables and longitudinal follow-up. In addition to demographic risks, several biomarkers have been evaluated for their association with CKD disease severity and progression. This chapter will review conventional biomarkers, novel biomarkers, and recently validated risk scores for predicting CKD progression and outcomes (Tables 5.1 and 5.2).

Individual Predictors of CKD Progression

Biomarkers are biological parameters used to differentiate between normal and abnormal physiological processes. For patients with CKD, biomarkers may reflect changes in renal function and thus may aid in predicting health outcomes, specifically progression of CKD or development of CVD [11]. There are conventional biomarkers that have been utilized for many years as well as newer, more novel markers to predict CKD progression.

Conventional Biomarkers

Estimated Glomerular Filtration Rate

Perhaps the best indicator of future CKD progression is current burden of CKD. It has been appreciated for several decades that once glomerular filtration rate (GFR) has decreased to below a critical level, CKD tends to progress

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Table 5.1 Prediction of chronic kidney disease [10].

Marker	Recommendation	Certainty of evidence	Strength of recommendation
KDOQI	Simple calculation of risk from eGFR and proteinuria	Observational studies	Strong
KRFE	Risk prediction using three, four, or eight variables	Validated in multiple large cohorts	Moderate/strong
MCMC	Risk prediction using nine clinical variables	Validated in multiple large cohorts	Moderate/strong

Table 5.2 Prediction of cardiovascular disease.

Scoring	Recommendation	Certainty of evidence	Strength of recommendation
eGFR	Independently associated with risk of CVD	Multiple observational studies	Strong
Proteinuria	Independently associated with CVD risk and outcome	Multiple observational studies, several RCT aimed a decreasing proteinuria	Strong

toward ESRD and is therefore the best indicator of global kidney function [12–15]. This observation suggests that the loss of a critical number of nephrons provokes a vicious cycle of further nephron loss. The natural history of CKD has been described with large variability depending on definitions, the population being studied, as well as the healthcare environment [16, 17]. Using estimated GFR (eGFR) as a marker of progression to ESRD, the African American Study of Kidney Disease and Hypertension (AASK) was able to identify three distinct patterns of CKD progression: (i) stable/increasing eGFR (less than 2 ml/min/1.73 m^2 decrease per year), (ii) rapid decrease in eGFR (a loss of more than 4 ml/min/1.73 m^2 per year), and (iii) alternating combinations of the previously mentioned categories. The most common pattern found in patients with CKD was a stable/increasing eGFR, with 58% of patients falling under this category [18]. The fact that only a minority of patients will develop ESRD further supports a need for risk stratification development in order to appropriately allocate treatment decisions. Almost all models that attempt to predict renal functional decline include an assessment of eGFR as a critical factor.

Albuminuria/Proteinuria

Proteinuria is another index of kidney disease severity in CKD patients, as it often results from glomerular injury [11]. In several longitudinal studies of patients with CKD, higher baseline proteinuria was indicative of a rapid decline in GFR [16–22] In a similar manner, baseline urinary albumin/creatinine ratio (ACR) in patients with diabetic nephropathy was found to be a strong indicator of ESRD [23, 24]. Proteinuria itself may pose as a risk factor for CKD progression, as one study using dipstick urinalysis concluded that proteinuria was the most predictive biomarker of ESRD risk over a 10-year period [25]. In many glomerular diseases, changes in proteinuria have also been associated with changes in renal prognosis, though these associations have not always been consistent. As with eGFR, the prognostic role of proteinuria/albuminuria is well established and it should be considered as a potent biomarker of CKD progression. As depicted in Figure 5.1, the 2012 Kidney Disease Improving Global Outcome (KDIGO) color-coded prognosis chart includes only eGFR and degree of albuminuria in risk assessment [26, 27].

Hypertension

Hypertension is common in both adults and children with CKD [28, 29]. Among patients with CKD, those with higher blood pressure have significantly faster GFR decline and the presence of hypertension has consistently been associated with rapid progression [17, 29–32]. This finding has led to recommendations regarding more intensive management of hypertension in patients with CKD [33]. While blood pressure appears to impart a deleterious effect on CKD progression in a continuous fashion without a specific "threshold" value, for convenience most prediction models that include blood pressure as a factor simply dichotomize blood pressure to hypertensive or not.

Serum Bicarbonate/Metabolic Acidosis

Metabolic acidosis is another common consequence of CKD and often causes impaired renal acid clearance [34].

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Guide to Frequency of Monitoring (number of times per year) by GFR and Albuminuria Category				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to midly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–300 mg/g 3–30 mg/mmol	>300 mg/g >30 mg/mmol
GFR categories (ml/min1.73 m^2) Description and range	G1	Normal or high	≥90	1 if CKD	1	2
	G2	Midly decreased	60–89	1 if CKD	1	2
	G3a	Mildly to moderately decreased	45–59	1	2	3
	G3b	Moderately to severely decreased	30–44	2	3	3
	G4	Severely decreased	15–29	3	3	4+
	G5	Kidney failure	<15	4+	4+	4+

Figure 5.1 Prognosis of CKD dependent on eGFR and degree of albuminuria, with recommended frequency of follow-up. Green, low risk (if no other markers of kidney disease, no CKD); yellow, moderately increased risk; orange, high risk; red, very high risk. *Source:* KDIGO [26]. © 2013 KDIGO

The majority of relevant studies have indicated that lower serum bicarbonate levels, even within normal range, are independently associated with CKD progression [7, 35–40]. Bicarbonate supplementation as a treatment for metabolic acidosis, either as oral sodium bicarbonate or a diet rich in fruits and vegetables, has been shown to decrease the rate of GFR decline in multiple small single-center studies [38–40]. Recent studies have shown that metabolic acidosis has additional end organ effects including impacts on cognition and endothelial function; new nonalkali treatments for metabolic acidosis are currently under development [35, 41–44].

Serum Phosphate and FGF23

Various studies have indicated that elevated serum phosphate levels are independently associated with renal injury in CKD [7, 45, 46]. However, this has been contradicted by a large study including 10 672 CKD patients, which found no association between higher serum phosphate and risk of progression toward ESRD [47]. Though not a conventional biomarker in clinical practice, phosphatonin fibroblast growth factor 23 (FGF23), a hormone involved in calcium and phosphate regulation, has also been suggested as an independent predictor of CKD progression [48, 49]. Elevated levels of FGF23 in CKD patients were independently associated with progression to ESRD, as well as cardiovascular events [50–52].

Uric Acid

Another biomarker which has been used to predict CKD progression is serum uric acid level [53–56]. An evaluation of children and adolescents in the Chronic Kidney Disease in Children Study (CKiD) cohort revealed that hyperuricemia is associated with a more rapid renal decline [56]. Compared to subjects with the lowest uric acid levels, those with intermediate and frankly elevated uric acid experienced a more rapid decline in eGFR. Uric acid levels remained significantly associated with progression even when controlling for other risk factors such as hypertension, proteinuria, initial GFR, and glomerular etiology, all of which were also significant in multivariate analysis. A 2018 meta-analysis of adults with CKD analyzed several randomized controlled trials (RCTs) done to evaluate the effects of uric acid lowering therapy on the disease progression [53]. The analysis included a total of 832 subjects with CKD randomized to uric acid lowering treatments versus placebo. Active treatment conferred a 3.88 ml/min/1.73m^2 (1.26–6.49 ml/min/1.73m^2) mean difference in eGFR. Additionally, risk of worsened kidney function or ESRD or death was significantly reduced with uricosuric pharmacotherapy. These data suggest that elevated uric acid represents a risk prediction tool and potentially a therapeutic target to slow CKD progression.

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Novel Biomarkers

Recently, a number of novel biomarkers have emerged as potentially new clinically-relevant risk prediction tools, but more research is needed to determine their full impact on CKD progression. For example, although levels of *neutrophil gelatinase-associated lipocalin (*NGAL*)* have been found to be overexpressed in patients with AKI [57] and are highest in CKD patients [58], the Chronic Renal Insufficiency Cohort (CRIC) study found that while urinary NGAL levels were independently associated with ESRD, they did not significantly improve prediction of CKD progression over predictions using only eGFR decline and proteinuria [59]. The *glycoprotein kidney injury molecule-1 (*KIM-*1)* is usually only present in the urine of patients with AKI or CKD [60]. One study found that serum KIM-1 levels increased with CKD progression and were independently associated with ESRD [61]. Through the Multi-Ethnic Study of Atherosclerosis, it was also determined that doubling of urinary KIM-1 levels was associated with an eGFR decrease greater than 3 ml/min/1.73 m^2 per year [62]. Elevated levels of *soluble urokinase-type plasminogen activator receptor (*suPAR*)* have also been observed in patients with renal disease, specifically glomerulosclerosis [11]. One study investigating suPAR determined that higher baseline levels were independently associated with CKD. Despite this, 30% of patients with a normal eGFR (>90 ml/min/1.73 m^2) were also found to have increased baseline suPAR levels, indicating that elevation may be a result of other biological processes, such as inflammation [63]. Lastly, the kidney-specific *glycoprotein uromoduliun (*UMOD*)* is known to have gene variants associated with eGFR decline and is associated with the development of CKD. One genome-wide association study using data from 3203 Icelandic CKD patients discovered a variant adjacent to the UMOD gene on chromosome 16p12 had an association with CKD and increasing creatinine levels [64, 65]. However, another study found that among 879 individuals of the Heart and Soul Study, UMOD single-nucleotide polymorphism variants influenced UMOD levels, but not CKD development [66].

The Role of AKI in Predicting Future CKD

Historically, clinicians assumed that patients who completely recovered from acute kidney injury (AKI) would regain baseline renal function. However, recent studies have contradicted this by demonstrating that a previous history of AKI is indeed associated with an increased risk of CKD and associated mortality [67]. To assess this association, one study looked at 343 AKI patients with a preadmission eGFR greater than 45 ml/min/1.73 m^2 who survived for at least 30 days after discharge without dialysis. The authors concluded that those who required dialysis for their AKI during hospital admission had a 28-fold increase in the risk of developing CKD stage 4 or 5, and had more than double the risk of mortality when compared to those who did not need dialysis [68].

Due to increasing evidence indicating the high likelihood of CKD development in post-AKI patients, there are ongoing efforts to develop a risk prediction model to identify which of these patients are at the highest risk. Using a cohort of 5351 patients diagnosed with an AKI, risk prediction models were developed that utilized variables of age, serum albumin, diabetes, baseline eGFR, mean serum creatinine, and severity of AKI as assessed by the RIFLE score (risk, injury, failure, loss, and end-stage kidney disease) or need for dialysis, non-African American ethnicity, and time spent at risk. External validation was performed using 11 589 patients admitted for pneumonia or myocardial infarction (MI), and yielded good prediction accuracy (area under the receiver operating characteristics [AUROC] value = 0.81–0.82) [69]. Further investigations are required that specifically include study populations with a higher proportion of women before clinical implementation.

CKD Risk Scores

Clinical prediction rules or models (sometimes called clinical decision tools) are tools that are created to assist clinicians in patient-level decisions [70–72]. Designed by multivariate analysis, these scoring models complement clinical decision making by suggesting diagnostic or therapeutic actions or providing prognostication of some clinical outcome. The goal of validated models is to improve individual patient outcomes and the cost-effectiveness of care [71]. Development of a clinical prediction model involves multiple steps, including (i) identification of important predictor variable (listed above in the case of CKD), (ii) assigning relative weights to each factor to create a combined score, (iii) assessing the score's predictive ability, including calibration and discrimination, and then (iv) validation of the model using both internal and external data.

Calibration is the agreement between the predicted probability of the outcome of interest and the observed frequency. It is usually plotted graphically as the observed outcome frequency against the mean predicted outcome probability (or risk). Goodness of fit for calibration can

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then be statistically tested. Discrimination refers to a model's ability to distinguish individuals who have the model outcome from those who remain event free, usually reported as the area under the receiver operating characteristic (ROC) curve (logistic regression c-statistic.) Models usually perform well within the data sample they are developed, as is often demonstrated using internal validation. External validation, therefore, is advocated to ascertain utility of the model in clinical practice. Several techniques of external validation are available [70, 73]. For a more comprehensive review, Moons and colleagues provide an in-depth analysis of clinical decision models in a two-article series [70, 71].

Investigation of risk factors/biomarkers used in predicting the development and/or progression of CKD has resulted in the discovery of a relatively small number of risk factors common to different forms of CKD. These risk factors are currently routinely being used to guide routine clinical practice, for example the revised KDIGO risk classification system uses GFR and albuminuria to categorize patients into CKD stages [26, 74]. This has led to the development of renal risk scores, which have the potential to be used in predicting the development and progression of CKD. Progress has already been made in developing a variety of risk scores to facilitate more accurate risk prediction, applying to those with and without CKD. We will now review several models that have been developed to predict risk.

The Kidney Failure Risk Equations

To predict the progression toward ESRD in patients with CKD, Tangri and colleagues developed the Kidney Failure Risk Equations (KFREs) in 2011, using data from a cohort of 3449 patients with late stage CKD [7]. Variables used in the eight-variable equation were age, sex, eGFR, albuminuria, serum calcium, serum phosphate, serum bicarbonate, and serum albumin. Simpler three-variable (age, sex, and eGFR) and four-variable (age, sex, eGFR, and albuminuria) models were also developed. While both of these simplified models performed well (Table 5.3), the eight-variable model performed best with respect to discrimination, calibration, and reclassification in an external validation cohort.

To assess the global functionality of the KFREs, a validation study of the equations was performed using 35 cohorts consisting of 720 000 patients with late-stage CKD across four continents. After a 4-year follow-up, the KFREs achieved accurate estimation of 23 829 cases of ESRD (c-statistic 0.90, 95% confidence interval [CI] 0.89–0.92 at 2 years; c-statistic 0.88; 95% CI 0.86–0.90 at 5 years). It was also found that the simplified four-variable equation produced similar discrimination compared to the eight-variable equation (c-statistics were 0.89 vs. 0.90 at 2 years and 0.86 vs. 0.88 at 5 years, respectively) [75].

Table 5.3 Hazard ratios and goodness of fit for sequential models in the development data set for three, four, and eight-variable kidney failure risk equations (KFREs).

Variable	Three-variable model	Four-variable model	Eight-variable model
Baseline GFR, per 5 ml/min/1.73 m^2	0.54	0.57	0.61
Age, per 10 years	0.75	0.8	0.82
Male sex	1.46	1.26	1.16
Log spot urine ACR[a]		1.60	1.42
Serum albumin, per 0.5 g/dl			0.84
Serum phosphate, per 1.0 mg/dl			1.27
Serum bicarbonate, per 1.0 mEq/l			0.92
Serum calcium, per mg/dl			0.81
c-statistics	0.89	0.91	0.92
Akaike Information Criterion[b]	4834	4520	4432
P value	<0.001	<0.001	<0.001

[a] Hazard ratio for ACR represents a 1.0 higher ACR on the natural log scale. For the average patient with 20 mg/g of albuminuria, this represents an increase to 55 mg/g.
[b] Null values for c-statistic and Akaike Information Criterion are 0.50 and 5569, respectively. Higher values for c-statistic and lower values for Akaike Information Criterion indicate better models.
Source: Tangri et al. [7]. © 2011 American Medical Association.

Newer Prediction Models

Several newer prediction models have also been developed and some are now available online. In 2018 Grams et al. developed models using data from over 250 000 individuals across 30 countries who participated in the international CKD Prognosis Consortium with eGFR < 30 ml/min/1.73m^2 [76]. The Markov Chain Monte Carlo (MCMC) model predicts 2- and 4-year risk of renal replacement therapy, cardiovascular (CV) event, or any cause of death using nine common predictor variables: age, sex, ethnicity, eGFR, systolic blood pressure, ACR, and any history of smoking, diabetes, or prior CVD (available at

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http://ckdpcrisk.org/lowgfrevents). This new model has significant overlap with KFRE (age, sex, eGFR, and albuminuria), though the additional variables provide an improved predictive ability in validation trials (within cohort R2 ranged from 0.89 to 0.97). A comparison of the predicted versus observed outcomes in various trials using both KFRE and the Grams MCMC model is shown in Figure 5.2 [76].

Successful clinical implementation of risk models requires both a validated risk prediction model and determination of absolute risk thresholds. Using these to guide therapy decisions will allow for a cost-effective treatment plan. Figure 5.3 demonstrates both the eGFR criteria (top) and the suggested KFRE risk-based thresholds (bottom) that prompt transition between different levels of care [77].

Transition from Primary Care to Nephrology

Patients with CKD will often develop hypertension and anemia, which are often managed under the supervision of primary care physicians [78]. However, these patients may be at higher risk for developing ESRD, resulting in a need for referral to nephrology in order to delay CKD progression, in turn preventing dialysis and reducing mortality risk [64, 79]. Implementing risk equations in the primary care setting may guide the appropriate timing of nephrology referrals. The 2012 KDIGO guidelines include recommendations for referral to specialty care, though the utility of this recommendation has not been subject to critical review [26].

Some have argued that if patients have a moderately reduced eGFR, they should be monitored at 3- or 6-month

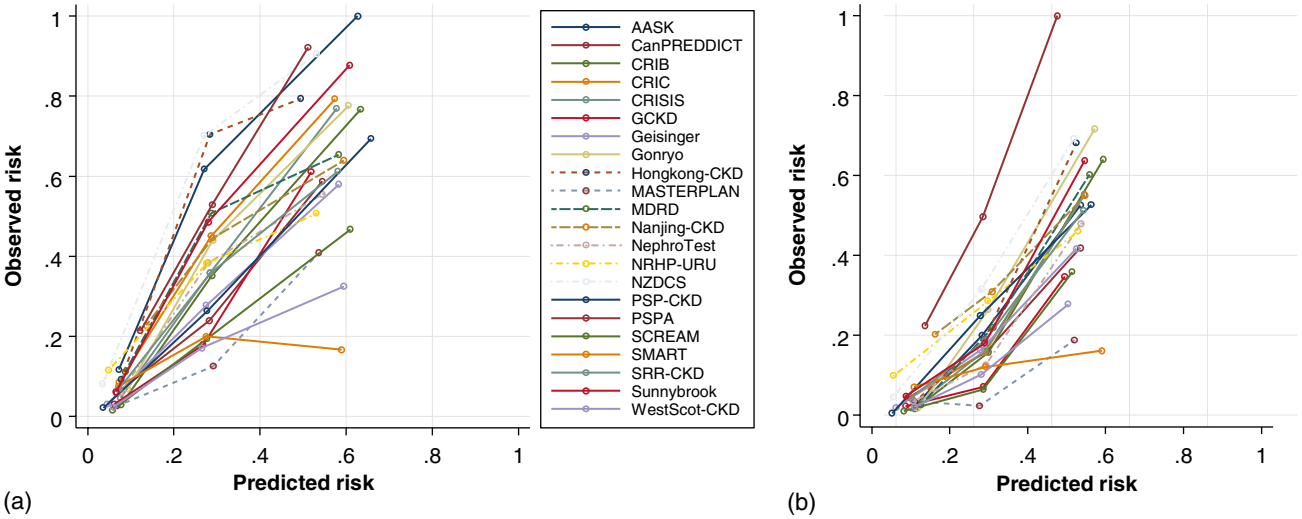

Figure 5.2 Calibration of the predicted versus observed 2-year risk of ESRD for (a) the kidney failure risk equation (KFRE) and (b) the MCMC model. Points represent groups of participants with <20% predicted KFRE risk, 20–40% predicted KFRE risk, and >40% predicted KFRE risk. *Source:* From Grams et al. 2018 [76].

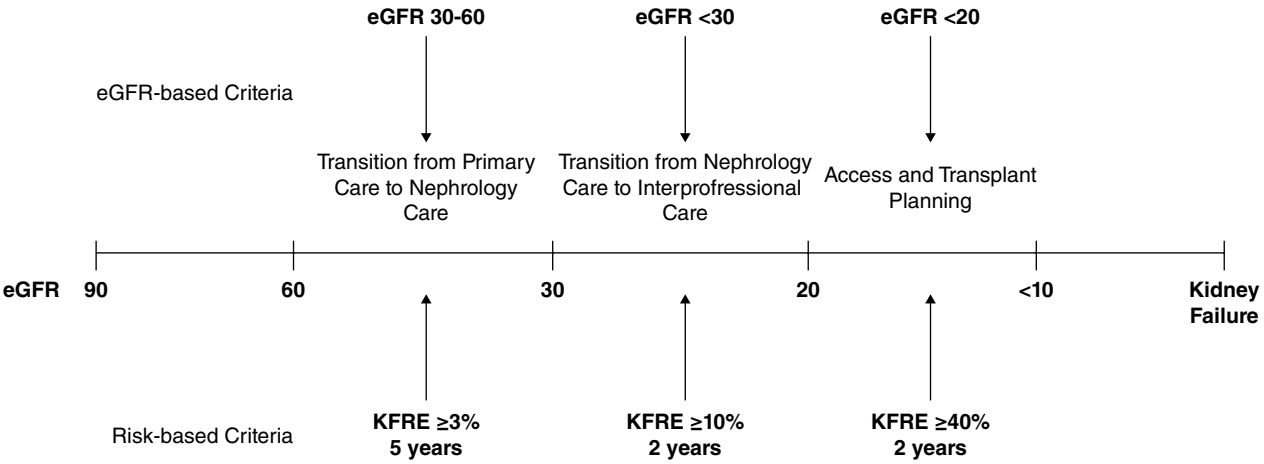

Figure 5.3 Traditional paradigm whereby eGFR values are used to determine intensity of care and inclusion of specialists in patients with CKD. *Source:* From Tangri N et al. 2017 [77].

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intervals, whereas those who are at a lower risk can be followed on an annual basis [80]. The KDIGO recommended frequency of follow-up is depicted in Figure 5.4.

Interdisciplinary Care

Interdisciplinary nephrology-led teams, which include nursing, pharmacy, and dietetic professionals, may improve the course of treatment, in turn ensuring timely dialysis initiation and lowering mortality risk. Ideally risk stratification would ensure these teams are not overburdened with low-risk CKD patients, thereby preventing inappropriate allocation of limited healthcare resources [18]. Following issues with excess demand for interdisciplinary care in Ontario, Canada, the Ontario Renal Network adopted a risk-based cutoff for clinical resource eligibility. The cutoff for interdisciplinary care was a 2-year risk of ESRD exceeding 10% or an eGFR less than 15 ml/min/1.73 m^2. As a result, the number of patients eligible was drastically lowered, as the previous threshold was solely based on an eGFR of less than 30 ml/min/1.73 m^2. Due to the implementation of this criterion, a proportion of patients with an eGFR between 30 and 45 ml/min/1.73 m^2 were also found to be eligible as they had a high risk of ESRD development. As a result of this change in cutoff, $6 million was saved annually for the healthcare system [81]. In the United States, the opposite may be happening with unacceptably late nephrology referral.

Dialysis Access and Modality Planning

It is currently the standard of care to recommend dialysis modality planning to patients with an eGFR less than 30 ml/min/1.73m^2, despite the fact that the majority of these patients will never progress to ESRD [82]. The weighing of risks and benefits when it comes to modality planning (hemodialysis vs. peritoneal dialysis) is paramount. The process of dialysis planning, including the creation of an arteriovenous fistula (AVF), the standard method of access for patients on hemodialysis, however crucial, may create anxiety for patients and caregivers. Furthermore, older adults are at a higher risk of AVF failure and subsequent adverse events, including heart failure and steal syndrome. Additionally, older adults who are at a low risk of progressing to kidney failure often have competing morbidities, further discouraging AVF formation [83]. By implementing risk prediction models such as the KFRE, AVF insertion can be guided properly to avert some of these risks while providing optimal treatment to low-risk CKD patients. The efficacy of implementing KFREs was simulated in 2014 using the Sunnybrook hospital cohort. The study concluded that a cutoff of 20% annual risk of

GFR categories (ml/min1.73 m^2) Description and range				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to midly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–300 mg/g 3–30 mg/mmol	>300 mg/g >30 mg/mmol
	G1	Normal or high	≥90		Monitor	Refer*
	G2	Midly decreased	60–89		Monitor	Refer*
	G3a	Mildly to moderately decreased	45–59	Monitor	Monitor	Refer
	G3b	Moderately to severely decreased	30–44	Monitor	Monitor	Refer
	G4	Severely decreased	15–29	Refer*	Refer*	Refer
	G5	Kidney failure	<15	Refer	Refer	Refer

Figure 5.4 KDIGO recommendations about referral to nephrology care in CKD. referral decision making by GFR and albuminuria. *a*Referring clinicians may wish to discuss with their nephrology service depending on local arrangements regarding monitoring or referring. *Source:* KDIGO [26] © 2013 KDIGO.

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ESRD calculated by the KFREs was more effective than eGFR-based cutoffs in predicting the need for AVF insertion and dialysis [84].

Predicting Cardiovascular Disease in CKD Patients

CKD substantially increases the risk of CVD in patients, but it is also itself a consequence of CVD. One study found that amongst hospitalized patients with congestive heart failure (CHF), the prevalence of late-stage CKD was 60.4% and it was 51.7% for those with MI [85]. When accompanying heart disease, CKD also increased the risk of mortality and ESRD in patients [86]. This may be a result of the shared risk factors of CVD and CKD, which include atherosclerosis, obesity, metabolic syndrome, hypertension, diabetes mellitus, dyslipidemia, and smoking. Renal atherosclerosis has been found in 39% of patients undergoing elective coronary angiography [87].

eGFR and Cardiovascular Risk

In the United States, individuals with CKD experience a 10-fold increased risk of vascular disease compared to those without kidney disease [88, 89]. This finding may be due to significant overlap of risk factors between CKD and CVD [90–92]. The excess CV mortality appears to begin early in the advancing CKD process and increases with worsened eGFR [76, 93]. Current CVD risk prediction models have proven to be unreliable when patients have concurrent CKD [94]. Bansal et al. developed a prediction tool that has shown promise in assessing 5-year mortality risk in patients with CKD but not ESRD (c-statistic 0.72, 95% CI 0.68–0.74). Their model incorporates age, sex, race, eGFR, urine ACR, smoking status, diabetes mellitus, and history of CHF or stroke. While this model has been externally validated in 789 participants (c-statistic 0.69, 95% CI 0.64–0.74), patients with CKD stages 4–5 were underrepresented in the validation study and therefore further investigation of this demographic is required prior to successful clinical implementation [95]. Researchers from Glasgow evaluated the effects of eGFR and proteinuria on CVD outcomes using data from 440 526 participants in the UK Biobank [96]. Their simple prediction model, created in 2019, uses different eGFR to predict CVD. The most successful model used cystatin C-based eGFR.

Proteinuria/Albuminuria and Cardiovascular Risk

Proteinuria/albuminuria predicts not only renal progression but is an ominous marker of other outcomes as well, most notably cardiovascular events. Multiple analyses have since established that ACR predicts all-cause mortality and cardiovascular death independent from baseline CKD and other covariates [97–101]. Early studies revealed a link between degree of microalbuminuria and poor outcomes in patients with type 2 diabetes [102]. Analysis of Framingham participants revealed that proteinuria predicted poor outcome in the general population as well [103]. Hillege analyzed a Dutch cohort of 40 548 adults and found a dose–response relationship between urinary ACR and both CV and non-CV mortality [98].

Future Considerations

Although some disagreement on the validity of various risk factors discussed in this chapter still remains, a relatively small group of risk factors appear to be common to most current studies. As a result, much progress has been made in developing risk scores based on these select variables in their ability to aid in predicting the progression of CKD, and with the development of risk prediction models. Future studies should focus on a more critical review of the aforementioned biomarkers and genetic factors utilized in risk score development, although the costs of measuring such markers is likely to be much higher than simple risk factors used at the present time. Accurate risk scores can align risk and resources, while allowing for personalized care for patients with CKD. Therefore, it is imperative to implement these risk scores into routine clinical practice, in turn helping patients and clinicians navigate the transition from CKD to dialysis.

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6

Chronic Kidney Disease in Disadvantaged Populations

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Introduction

Chronic kidney disease (CKD) is an established global public health problem that represents a key determinant for poor health outcomes [1–4]. In recent decades it has been increasingly recognized that CKD is more frequent and has poorer outcomes among populations or communities considered "disadvantaged" in both the developed and developing world [1, 5–8]. Such communities include "ethnic, socio-economically deprived, and other minority groups that are at greater risk of developing CKD," according to the International Society of Nephrology [9]. The causes of CKD in disadvantaged populations are varied and reflect exposures to environmental, socioeconomic, and other factors that contribute to a reduction in nephron mass over time. In any one individual, perinatal factors, nutritional factors, exposure to toxins, and infections may all contribute to the development of CKD. The entity CKD of uncertain etiology (CKDu) is one condition that is over-represented in disadvantaged populations.

Apart from being more frequent, kidney disease among disadvantaged populations tends to be underdiagnosed. When detected, access to care is limited and, frequently, suboptimal [8]. Irrespective of the underlying cause of CKD, the combination of those two factors – underdiagnosis and suboptimal treatment – contributes to poor clinical outcomes. Moreover, the development of end-stage kidney disease (ESKD) in communities in which access to renal replacement therapy (RRT) is limited or nonexistent forces households to incur substantial out-of-pocket expenses, perpetuating the poverty cycle. Additionally, disadvantaged populations are a recurrent source of organ donors for other populations, frequently victims of illegal traffic practices, which contributes to the depletion of an already scarce pool of grafts available to disadvantaged persons.

Given the complexity and systemic nature of this problem, the required interventions are interdisciplinary and multidimensional. Therefore, it is not only a matter incumbent to the medical community. Only global-scale efforts involving multiple stakeholders will be able to close the observed gaps in kidney care that disadvantaged populations experience. Key partnerships between governments, nongovernmental organizations, researchers, and clinicians are paramount to achieve an improvement in outcomes. The World Health Organization (WHO) has established sustainable health goals that are only possible with a concerted multidisciplinary approach. This chapter presents the available evidence of the distribution of CKD in disadvantaged populations across the globe, with a particular focus on the challenges and opportunities in the detection and treatment of CKD among such populations.

Epidemiology

According to a recent meta-analysis that pooled data from 100 studies of diverse quality comprising 6 908 440 patients, an estimated 11% of people worldwide are affected with CKD stages 3–5 [10]. Table 6.1 shows the CKD prevalence estimates for different regions in this study. The prevalence of CKD varied substantially across regions, which was partially attributable to substantial heterogeneity between the studies included as well as differences in quality.

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Table 6.1 Estimated prevalence of CKD in specific countries.

	CKD prevalence (%, 95% CI)			
	Stages 1–5		Stages 3–5	
Region	***N***	**Prevalence (%)**	***N***	**Prevalence (%)**
South Africa, Senegal, Congo	5497	8.6 (1.3–16.0)	1202	7.6 (6.1–9.1)
India, Bangladesh	1000	13.1 (1.0–15.2)	12 752	6.8 (3.7–9.9)
Iran	17 911	17.9 (7.4–28.5)	20 867	11.7 (4.5–18.9)
Chile	0	–	27 894	12.1 (11.7–12.5)
China, Taiwan, Mongolia	570 187	13.2 (12.1–14.3)	62 062	10.7 (6.6–13.5)
Japan, South Korea, Oceania	654 832	13.7 (10.8–16.7)	298 000	11.7 (5.3–18.1)
Australia	12 107	14.7 (11.7–17.7)	896 941	8.1 (4.5–11.8)
USA, Canada	20 352	15.5 (11.7–19.2)	1 319 003	14.4 (8.5–20.3)
Europe	821 902	18.4 (11.6–25.2)	2 169 183	11.9 (9.9–13.8)
Global		13.4 (11.7–15.1)		10.6 (9.2–12.2)

Source: Reproduced from Hill et al. [10]. © 2016 Hill et al. Licensed Under CCBY 4.0. This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Nonetheless, the observed differences can also be explained by true variations in the prevalence of kidney disease among regions. Remarkably, the global prevalence of CKD appears to be higher than that of diabetes, which has been reported to be about 8.8% [11], underscoring the relevance of CKD to global health.

Another study that pooled data from 33 reports with gender- and age-specific prevalence of CKD in representative population samples estimated that nearly 500 million individuals have CKD, of which almost 80% live in low-middle-income countries (LMICs) [12]. Importantly, the age-standardized prevalence of CKD was higher in men and women from LMICs when compared to men and women from high-income countries. Despite the observed disparities between developed and developing countries, the epidemiological trends of CKD in LMICs, including the causes of kidney disease and their distribution across the population, are either unknown or poorly characterized [13, 14]. There are reasons to believe that the causes of CKD are widely heterogeneous in LMICs. As a result of an accelerated demographic transition and urbanization, most of these countries have experienced an unprecedented upsurge in noncommunicable diseases [15]. A sedentary lifestyle and unhealthy diet are intertwined in densely crowded cities with limited public health and heathcare infrastructure, resulting in high rates of underdiagnosed and suboptimally treated hypertension and diabetes. These populations are enormously vulnerable for adverse kidney outcomes. For instance, reports from Mexico City show that CKD is strikingly frequent among population with diabetes [16]. A prospective analysis of a large cohort in this population recently reported that adults (35–84 years) with diabetes had a 20-fold higher risk of dying from kidney disease compared with those without diabetes [17]. This excess risk is most likely due to suboptimal management of diabetes: those with diabetes had a mean glycated hemoglobin of 9.0% and poor glycemic control was associated with increased mortality risk [18].

The etiology and epidemiological determinants of kidney diseases in areas like Africa, Asia, and Latin America differ from what is observed in Europe and North America and even within regions can vary substantially [14]. As shown in Table 6.2, apart from diabetes and hypertension, communicable diseases such as HIV, malaria, and schistosomiasis may be important contributors to the burden of CKD in sub-Saharan Africa, even though evidence of their attributable fractions is limited or absent [19, 20].

Definitions and Theoretical Framework

According to the WHO, social determinants of health (SDH) are defined as "the conditions in which people are born, grow, live, work and age" [21]. SDH are mostly responsible for health inequities, "the unfair and

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Table 6.2 Environmental factors associated with CKD.

Factor	Description
Heavy metals	*Lead*: particularly important in LMIC; contained in paint, gasoline, adulterated gasoline, contaminated food and water, soil, mines, garages *Cadmium*: sources include tobacco, batteries, fuel, industrial waste, certain South-Eastern Asian medicinal herbs or foods *Arsenic*: fish contamination, fuel, cereals treated with ethyl mercury as pesticide *Uranium*: contaminated food or water
Other toxins	*Aristolochic acid* associated with chronic tubulointerstitial nephritis and urothelial cancer; the causal agent of Balkan endemic nephropathy Exposure to other *chemicals* used for consumer activities or medical treatment; industrial chemicals; occupational chemicals apart from heavy metals (e.g. methylene chloride, trichloroethylene, toluene); most associated with acute disease and/or accentuated progression of underlying disease
Occupational exposures	*Mesoamerican nephropathy* affecting agricultural workers; most likely mechanism consists in repeated subclinical episodes of AKI due to dehydration during work shifts; uric acid crystalluria might be involved in kidney damage; several other potential synergistic factors (e.g. NSAIDs, fructose-high beverages, alcohol consumption, pesticides) *Sri Lanka, India, and Pakistan*: contamination of water/food by unknown agent (industrial chemicals, agrochemicals, heavy metals suggested)
Medications	*NSAIDs* (linked with AKI, but not yet with CKD); mis-regulated alternative or novel therapies or medications (usually counterfeit); *herbal remedies*
Infections	Related to poor hygiene conditions in LMICs; parasites (e.g. schistosomiasis, malaria, leptospirosis, tuberculosis, etc.); enteric and diarrheal diseases; HIV-associated nephropathy; hepatitis B and C viruses

avoidable differences in health status seen within and between countries" [21]. Therefore SDH, and the resulting disparities in health, are key components of what is considered a "disadvantaged population" [22, 23]. However, the definition most widely accepted for "disadvantaged population" is not restricted to those at a greater risk of kidney disease due to SDH, and further includes "ethnic, socio-economically deprived, and other minority groups" [9]. Even though the definition of minority groups largely derives from sociodemographic phenomena (i.e. the definition of a minority is relative to a majority in a population), [24] the concept of ethnicity is closely related with genetic ancestry and, subsequently, with a complex cluster of social and biological factors. The definition of "disadvantaged populations" can therefore be ambiguous, as a myriad of factors can predispose individuals and populations to kidney disease. Three main factors, however, can be identified as underlying and sometimes overlapping causes of disadvantage: (i) socioeconomic factors that affect health behavior and access to care, (ii) biological factors that predispose to adverse kidney outcomes, and (iii) environmental factors, e.g. labor conditions and exposures to nephrotoxic agents. These factors are not necessarily a direct cause of kidney disease but may act as mediators on the causal pathway (Figure 6.1).

Socioeconomic Factors

Socioeconomic status (SES) usually encompasses education, occupation, and income as proxies for measurement of social and economic wellbeing. Lower SES has consistently been associated with increased morbidity and all-cause mortality [25]. Frequently, access to health – frequently measured as insurance status – and risk behaviors have been suggested as the mechanisms explaining the link between SES and health. However, it has become clear that those factors do not fully account for the associations observed, and other more complex factors such as social isolation and adversity may be involved [22]. This is not different for CKD, where the incidence and prevalence of CKD and the progression of disease varies by SES, being higher at lower SES levels [26, 27]. For instance, low income or education below high school level have been associated with the presence of albuminuria in the United States [28]. In the Chronic Renal Insufficiency Cohort, lower income and education were associated with lower estimated glomerular filtration rate (eGFR) [29]. Progression of CKD into ESKD is more likely among individuals with low income and education [30–32]. Additionally, those with ESKD who have less education or are unemployed are less likely to receive a transplant [33, 34] and more likely to experience dialysis complications such as peritonitis [35, 36] or graft rejection if they receive a transplant [37]. Irrespective of the mediating factors in the association between SES and CKD, it is clear that a low SES confers a greater risk of developing CKD and having poor outcomes, and therefore such segments of the population can be considered disadvantaged.

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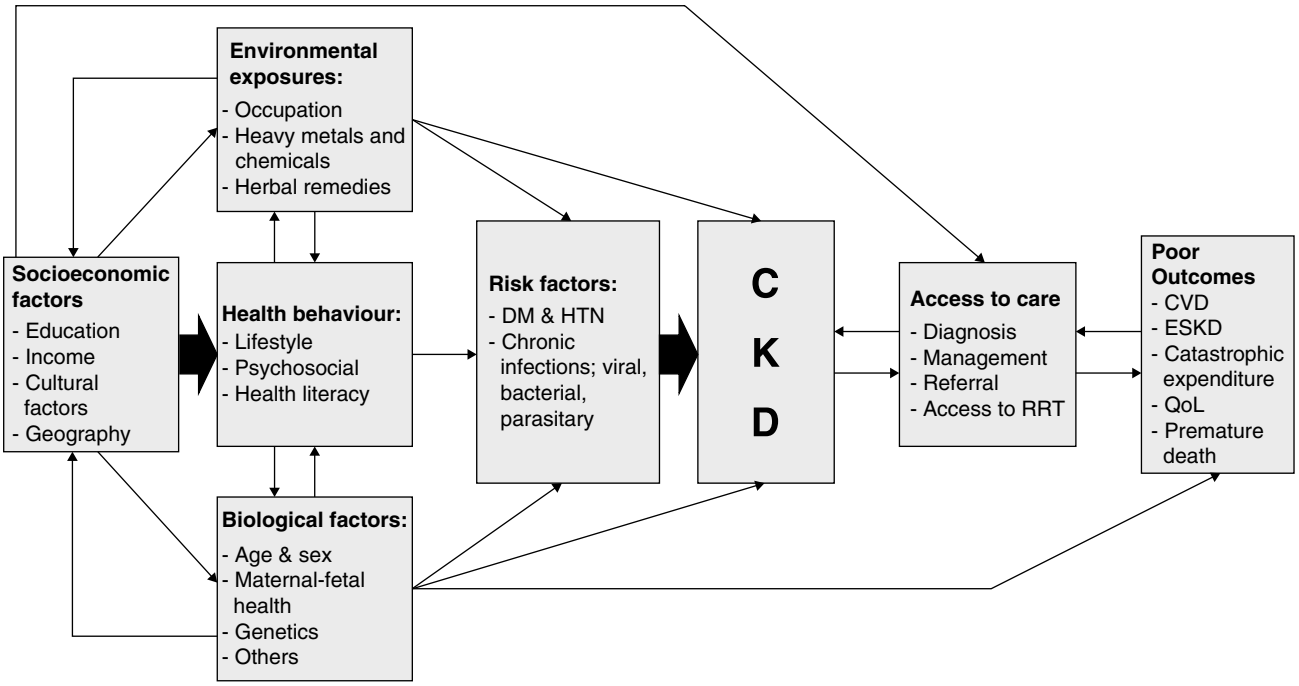

Figure 6.1 Theoretical model: interaction of socioeconomic, environmental, and biological factors and their impact on health behavior, risk factors, and direct causes of CKD, access to care, and outcomes. CKD, chronic kidney disease; CVD, DM, ESKD, end-stage kidney disease; HTN, QoL,

Environmental Exposures

Environmental exposures associated with the development of kidney disease are well known [38–40]. They include heavy metals such as lead, arsenic, mercury, and cadmium, other toxins such as the aristolochic acid (the cause of the Balkan endemic nephropathy), industrial and agricultural chemicals, occupational exposures, which are not fully delineated but appear to correlate with specific occupations (e.g. Mesoamerican nephropathy and agricultural workers), medications and herbal remedies, and infections (Table 6.3). Some of these factors have been recently linked with the emerging CKDu hotspots around the globe [38, 60]. Defined as "countries, regions, communities, or ethnicities with higher than an average incidence of CKD" [61], these hotspots are currently of major research interest, even though there is a paucity of evidence to establish a cause–effect relationship in most cases [13]. Importantly, most of these hotspots are located in LMICs with limited health resources, and thus are closely linked to socioeconomic factors. The cases arise mainly from socioeconomically deprived communities, mostly consisting of working-class individuals whose income directly depends on their ability to continue working in the very conditions that potentially expose them to kidney injury. Frequently, affected communities lack social security and have limited availability of public health protection programs. Associated with this deprivation comes a lack of health resources, both infrastructure and trained professionals. This limited capacity for systematic research has hindered efforts to accurately identify hotspots for disease and reliably estimate incidence rates [13, 44, 61].

Biological Factors

Apart from aging, there are two main determinants that predispose individuals to developing kidney disease and can be considered inherently biological: genetics and developmental programming. Genome-wide association studies and other novel sequencing techniques have identified at least 50 genetic regions or variants associated with adverse kidney outcomes and the development of CKD [62]. As genetic variants are inherently linked with ancestry and vary across populations, population-based genetic studies have given key insights into kidney function traits and have been helpful toward understanding the distribution of kidney disease in specific populations.

In the United States, a major disparity in CKD has long been documented between black and nonblack populations [56]. African Americans have historically had higher progression of diabetic and nondiabetic kidney disease. Even though African Americans represent about 13% of the US population, they comprise 33% of incident cases of ESKD. Moreover, the lifetime risk of ESKD in African Americans is an estimated 8.2% (compared with only 2.7% in European Americans) [57], with a disproportionate number of patients requiring RRT.

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Table 6.3 Description of identified CKD hotspots or disadvantaged populations with CKD.

Region	Cause or type of CKD	Comments	Certainty of evidence (GRADE)
Sub-Saharan Africa	HIV-related	HIV-related GN in countries with high prevalence of the infection [20]; certain genetic variants in the APOL1 gene may predispose to HIV-related nephropathy in African population [41]; the prevalence of CKD among populations with HIV is estimated to be around 12% in sub-Saharan Africa [19]	High ●●●●
	Malaria	Mostly caused by *Plasmodium falciparum* [20]; immune-mediated glomerular and tubular disease [42]; 250 million cases of malaria per year of which 90% in sub-Saharan Africa; 445 000 deaths in 2015, of which 91% in sub-Saharan Africa; renal involvement (i.e. AKI) in at least half of malaria deaths [42, 43] Limited evidence of a direct association of malaria and CKD	
Central America and Mexico	Mesoamerican nephropathy	Working conditions; unknown etiology; repeated episodes of acute kidney injury which evolve into overt CKD; possibly related with heat-stress, exposure to agrochemicals, use of NSAID and other over-the-counter drugs [13, 44, 45]	Low ●●○○
	Diabetic nephropathy	Unhealthy diet and sedentary lifestyle; high rates of overweight and obesity; high prevalence of diabetes with suboptimal management [17, 18]; high prevalence of CKD among those with diabetes and or hypertension, with most of them being undiagnosed [16, 46]; higher risks of kidney-associated death [17, 18]	High ●●●●
Southern Asia	Sri Lanka nephropathy	Chronic tubule-interstitial nephritis in agricultural and construction workers; unknown cause; exposure to cadmium through food chain and pesticides exacerbated by genetic factors [47] or selenium deficiency [48] suggested as possible causes; clinically similar to MeN [38]	Low ●●○○
	Andhra Pradesh, India	Coastal regions known as Udannam area; unknown cause; contamination of drinking water suspected, but no evidence found of chemicals above permissible limits [49]	
Oceania	Australian Northern Territory and Maori and Pacific communities in New Zealand	Higher incidence of CKD among rural aboriginal communities in central Australia; probably associated with higher prevalence of overweight and obesity as early as from childhood; a potentially strong role of developmental origins of disease [27, 50–52]	Low ●●○○
Europe	Balkan endemic nephropathy	Endemic along the Danube river Most likely cause is consumption of aristolochic acid obtained from wheat frown in fields contaminated with *Aristolochia clematitis* [53–55]	Moderate ●●●○
North America	African-American communities	Genetic predisposition for CKD (APOL1 high-risk variants) in combination with health disparities [56, 57]	High ●●●●
	Hispanic agricultural workers	AKI among agricultural workers after workshifts; potentially similar to MeN [58, 59].	Low ●●○○

AKI, acute kidney injury; CKD, chronic kidney disease; MeN, NSAID,

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It was recently discovered that two coding variants of the *Apolipoprotein L1* (APOL1*)* gene on chromosome 22q13 were associated with higher rates of focal segmental glomerulosclerosis (odds ratio 10.5) and hypertension-attributed ESKD (odds ratio 7.3) [63, 64]. Interestingly, these two variants are common in individuals of recent African ancestry, mostly absent in European populations, and appear to be protective against African sleeping sickness as *Apolipoprotein* L-1 has an active lytic role in trypanosomes. Moreover, it has been proposed that these variants may be involved in the development of HIV-associated nephropathy [41], sickle cell kidney disease [65], and severe lupus nephritis [66].

Understanding the role of *APOL1* is paramount for assessing the burden of CKD among African Americans and, globally, in populations with African ancestry. It is estimated that about five million African Americans possess at least two *APOL1* nephropathy variants, which puts these populations at a higher risk of developing CKD. APOL1-associated kidney disease could potentially account for up to 40% of the total burden observed in African Americans [57]. The interaction of *APOL1* with environmental – potentially modifiable – risk factors and other genes represents a major area of interest for research that will allow a more detailed phenotyping of kidney disease, particularly in those individuals with poor response to therapies for blood pressure control and proteinuria reduction. The example of APOL1 underscores the important role that genetic factors may have in the burden of kidney disease and its clustering in specific populations. Research on interactions between genes and environment is still at an early stage, although it is an area of great interest for CKD hotspots. Some examples include Sri Lanka nephropathy and a single-nucleotide polymorphism in the SCL13A3 gene, which appears to predispose to CKD [47]. Likewise, a gene in 3q25 could explain the familial clustering of the Balkan endemic nephropathy [53]. Further studies are, however, still required to replicate and confirm such associations.

In addition to genetic and lifestyle factors as determinants of noncommunicable diseases, the "developmental origins of disease" has emerged as a comprehensive pathophysiological model of disease risk, which may be of particular relevance to the kidney [67]. This model proposes that individuals at greatest risk of kidney disease [68, 69] – as well as diabetes, [70, 71] hypertension, [72] and cardiovascular disease [73, 74] – are those who experienced adverse physiological conditions such as maternal malnutrition [75, 76] during gestation, resulting in low birth weight and underdevelopment of fetal kidneys. Furthermore, consequent rapid weight gain after birth is associated with childhood and adulthood obesity [77–79], a well-known risk factor for diabetes, hypertension, and kidney disease. Likewise, low birth weight, prematurity, and small size for gestational age have been associated with reduced nephron mass and an increased risk of developing CKD and hypertension in adult life [80]. The global impact of these risk factors is substantial. In LMICs, a total of 43.3 million deliveries were either premature or small for gestational age in 2010 [81], thus giving them a higher risk of developing noncommunicable diseases including kidney disease [67]. Albeit a reduced nephron number may not be sufficient to develop CKD in adult life, the interaction of such predisposition with high-risk genetic variants, environmental factors, and other stressors (e.g. episodes of acute kidney injury) may become relevant in a fraction of cases. A life course approach that assesses the interaction between genetics, perinatal, childhood, and adulthood exposures is likely to better inform our understanding of the development of CKD in disadvantaged populations [14, 44].

There are important gaps to be addressed in the understanding of biological factors and kidney disease [38]. First, education and awareness of clinicians, researchers, and patients is still limited. This is particularly relevant in terms of translation of research findings into therapeutics, as well understanding the attributable fraction of genetics to the overall burden of kidney disease. Second, the majority of genetic research is carried out in populations of European ancestry, even though indigenous and other disadvantaged populations have shown higher rates of kidney disease. This lack of diversity substantially hinders the generalizability of genetic findings, raises the issue of potentially misclassifying benign variants as pathogenic [82], and limits the understanding of kidney disease among disadvantaged populations. An improved knowledge of genetic and developmental determinants of kidney disease and their interaction with environmental factors may provide important insights into renal pathophysiology, which in turn could facilitate the development of more effective prevention strategies and pave the way for novel therapeutics.

Challenges in the Diagnosis of CKD Among Disadvantaged Populations

There are several challenges which need to be systematically addressed in the context of CKD in disadvantaged populations. These include lack of awareness, strategies for screening, workforce capacity, and availability of laboratory tests.

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Awareness

Lack of awareness is a major barrier to tackling the public health issue of CKD. This is particularly problematic in LMICs, where the majority of individuals with CKD go undetected [23]. It is estimated that only one-third of individuals with CKD are diagnosed worldwide [4]. A population-wide study in the United States in high-risk individuals reported that the prevalence and awareness of CKD were, respectively, 23.4% and 11.9% for Asians and Pacific Islanders respondents, 29.5% and 8.6% for European Americans, 20.3% and 11.1% for Hispanics, 22.8% and 6.3% for African Americans, and 29.2% and 6.8% for Native Americans [83]. A study in China reported that the prevalence and awareness of CKD were 5.7% and 1.0% [84], whereas in another study from this country, only 8% of rural Chinese individuals with CKD were aware of having the disease [85]. Finally, a study from Mexico reporting prevalence of CKD in high-risk populations showed that only 1% of the participants were aware of having CKD despite 71% of them having had a doctor's appointment in the last year [16]. Further reports show that the proportion of the CKD population that is aware of their condition is low in many other LMICs, including Tanzania (10%) [14], Senegal (23%), and Taiwan (3.5%) [86]. These data suggest that the gap in awareness is important in all populations, but may be substantially larger in LMICs.

Screening

A major challenge in the diagnosis of CKD is deciding if a screening program – either in the general population or restricted to high-risk individuals – is appropriate [87]. Wilson and Junger proposed 10 criteria in 1968 to help decision-makers in the implementation of screening programs. In disadvantaged populations, special consideration of the availability of diagnostic tools and treatment options that are affordable and sustainable must be prioritized. The arguments in favor of screening for CKD in disadvantaged populations are, first, that the burden is substantial, as shown by the observed high prevalence, the low rate of awareness, and unduly high risks of premature death and morbidity reported among such populations. Second, that the economic burden of CKD is substantial and appears to be higher in LMIC, for both households and health systems [4]. Third, the natural history of CKD is relatively well understood. The progression of CKD from its early stages to kidney failure ranges between 12 and 15 years, although the range can be variable [88]. This window allows for the implementation of effective strategies that can slow the progression of disease and/or prevent complications, such as treatment of hypertension, maintenance of good glycemic control, and the use of lipid-lowering therapy [89, 90]. There is, however, uncertainty surrounding CKDu hotspots since little is known about the natural history of disease and there is no evidence of the effectiveness of therapy. Nevertheless, the global consensus is that an early diagnosis is preferred with the objective of identifying the cause of kidney injury and preventing progression and the requirement of RRT [2].

Diagnostic Tools

A related challenge is the selection of tests for screening and diagnosis. There is very limited evidence to guide choices, and decisions should be based on local and regional resources as well as the cultural acceptability of each mode of testing. An initial approach with risk scores and questionnaires to identify high-risk individuals is potentially useful for large-scale screening. The models used for predicting the risk of having CKD and its progression are largely based on European or North American populations and often require measuring biomarkers. This is a major inconvenience in resource-poor settings where laboratory testing is not readily available [87, 91]. In addition, the diagnosis and staging of CKD require the measurement of both glomerular filtration rate and albuminuria [89], with multiple tests available. The quality of such tests in LMICs varies widely, with limited use of validated tools [19, 92]. These differences could potentially explain the heterogeneity observed in the estimates of CKD prevalence in these populations. In a 2014 systematic review and meta-analysis on the epidemiology of CKD in sub-Saharan Africa that included 90 studies from 96 sites, the measurement of urine protein was the most common method for determining the presence of kidney disease (62 out of 90 studies [69%]) [19]. Only 22 studies (24%) used the Cockcroft–Gault formula and 17 (19%) used the Modification of Diet in Renal Disease (MDRD) formula to eGFR. This study reported an overall prevalence of CKD of 13.9% (95% CI 12.2–15.7). Substantial variability was found between countries, with estimates ranging from 2% in Cote d'Ivoire to 30% in Zimbabwe. Apart from differences in sampling procedures, this heterogeneity was also attributed to differences in the measurement methods. One plausible solution to facilitate screening and diagnosis of CKD in resource-limited settings is the use of point-of-care tests for measuring creatinine [93] and albuminuria [94]. Although these methods are not as reliable as laboratory-based measurements, they offer advantages including prompt decision-making by the clinician, avoidance of time-consuming logistics for transportation of specimens (of major relevance for

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isolated tropical communities in which samples can be damaged by heat), and cost savings for patients through reductions in clinic visits.

Other Challenges

There are several additional challenges associated with diagnosing CKD in disadvantaged populations, including diversity in the underlying causes of kidney disease and a lack of consensus on diagnostic criteria for specific diseases, i.e. mesoamerican nephropathy and other cases of unknown etiology. The limited availability of reliable and validated measures of kidney function is compounded by a paucity of adequately trained health professionals, particularly in under-resourced communities.

Challenges and Opportunities in Treatment

Given the high costs associated with provision of RRT, the main focus of therapeutic interventions should be on CKD prevention, slowing disease progression, and avoiding complications.

Early Prevention Programs

These programs are centered on early and aggressive management of risk factors, and have been shown to be cost-effective for cardinal risk factors such as diabetes and hypertension [95]. Interventions may include early detection using low-cost tools such as albuminuria testing, and the use of renoprotective agents such as renin angiotensin aldosterone system blockers.

Access to Optimal Care for CKD

Limited access to primary care and specialist nephrology care is a common problem in LMICs. There is scope for international training programs to enhance capacity in CKD care in these countries, for example the fellowship opportunities provided by the International Society of Nephrology. In addition, efforts should be made to widen the availability and affordability of medications with proven benefit for CKD patients, such as antihypertensives and lipid-lowering medications.

Availability of RRT

ESKD in disadvantaged populations has an unduly poor outcome. A retrospective study in Nigeria that included 760 patients with incident ESKD showed that the majority were offered hemodialysis (73%), with only a small proportion having access to peritoneal dialysis (1%) or transplantation (<1%). The remaining 25% received conservative management due to unaffordability of dialysis or ongoing viral infection which precluded their access to hemodialysis. Moreover, only 5% of those who initiated hemodialysis were able to afford treatment for longer than 3 months [96]. A similar scenario has been described in India, where less than 10% of patients requiring RRT receive it and of those >70% die within the first 12 weeks due to inability to afford sustained treatment [97, 98]. Likewise, in Asian countries without funded renal programs, around 90% of patients with ESKD die within months of diagnosis due to a lack of access [60]. As the costs of dialysis rise to US$20000–100 000 per year [99], for a great proportion of individuals from disadvantaged communities RRT becomes prohibitively expensive.

A systematic review and meta-analysis that pooled data from 123 countries and included 93% of the worldwide population estimated that, in 2010, 2.618 million individuals received RRT, of which 2.050 million (78%) received dialysis and the remainder a transplant [8]. It was conservatively estimated that the number of patients needing RRT was 4.902 million, but it could be closer 9.701 million. Thus, between half (2.284 million, 47%) and up to three-quarters (7.083 million, 73%) of individuals requiring RRT worldwide did not receive it, which translated to at least 2.284 million premature deaths. Notably, an alarming disparity between the need for and the receipt of RRT was found in terms of income level. Of all those receiving RRT in 2010, 92.8% resided in high-income or high-middle income countries. This represents a striking 70-fold prevalence gradient [6]. By contrast, only 7.2% resided in low-income countries where 96% of the patients requiring RRT did not receive it. This proportion decreases to 88% in LMICs and 58% in high-middle income countries, which suggests that access to RRT is socially graded. The projections from this meta-analysis estimated that by 2030 the number of individuals requiring RRT will more than double to a total of 5.439 million, with the greatest increase in Asia and Africa, the regions where the population is expected to grow the most.

Unhealthy aging has been largely documented as the result of gains in economic development and increases in life expectancy in the developing world and is arguably the demographic reason pushing the expected increase in the demand of RRT. This is of relevance in those disadvantaged populations in which unhealthy behaviors have increased the prevalence of risk factors for CKD such as hypertension and diabetes. Countries must prepare their health systems to face the challenge ahead and meet the demands of RRT in the present and foreseeable future.

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RRT rationing resulting from limited facilities and resources in low and middle-income countries is complex. Key areas of opportunity in regard to RRT include establishing registries of dialysis and transplantation in all countries. Likewise, identifying patients who need RRT but do not receive it is important. Open sharing of methodology, sampling frameworks, and innovative strategies between countries could potentially facilitate this work in countries without a registry.

Health Literacy

Limited health literacy affects 25% of the population with CKD and this percentage is likely higher in disadvantaged populations and has been associated with adverse outcomes in CKD populations [100]. A recent meta-analysis that examined 13 studies found that limited health literacy was significantly associated with hospitalizations, emergency department use, missed dialysis sessions, cardiovascular events, and mortality [101].

Conclusion

CKD in disadvantaged populations is increasingly recognized in low-, middle- and high-income countries and is due in part to rising incidence and prevalence of hypertension and diabetes in those populations, as well as unique genetic, environmental, and socioeconomic factors. Implementation of effective prevention programs and improvements in quality of care for the diverse causes of kidney disease in each population is required. Such programs must be tailored to local requirements so that they can meet the epidemiological, cultural, and societal needs of the communities they serve, and ultimately translate into better clinical outcomes. Identifying the major risk factors in each community is paramount to maximize the efficacy of any intervention. Similarly, prioritizing low-cost interventions, such as albuminuria testing followed by treatment with blockers of the renin-angiotensin system or bicarbonate supplementation for metabolic acidosis, may have a significant impact on CKD prevention and disease progression. Only by tracking these outcomes can the implementation of practical interventions be appropriately evaluated. Inequity in health is at the very core of the observed disparities in CKD burden among disadvantaged populations. It is a moral imperative to solve the existing disparities, especially given the evidence that, in some cases, the lack of access to RRT is due to inefficient allocation of available resources rather than a lack of them [102]. The WHO has established sustainable development goals for universal health coverage. It is paramount that efforts from global health organizations are championed by researchers and clinicians at every level to achieve an improvement in CKD care worldwide.

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Part 2

Acute Kidney Injury

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7

Overview/Definition, Classification, and Epidemiology of Acute Kidney Disease

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Introduction

Acute kidney injury (AKI), previously known as acute renal failure, refers to a sudden reduction in kidney function. This acute reduction in kidney function typically manifests as a fall in urine output and/or a rise in blood urea nitrogen and creatinine, two blood biomarkers that are filtered and excreted by the kidney and are readily measured in the clinical laboratory. While initial descriptions of AKI focused on the most severe forms of disease, over the past 15 years there has been a growing recognition that small changes in serum creatinine are associated with adverse outcomes, including longer hospital length of stay and death. Thus, a major focus of the field for the past 15 years has been the development of consensus definitions and approaches to defining AKI. These have been important to moving the field forward because they have allowed comparison of studies across settings and disease subtypes.

In this chapter, we will review the consensus definitions for AKI, along with recent work to develop consensus regarding acute kidney disease (AKD) that does not meet the technical definition of AKI and recovery from AKI. We will also review common settings in which AKI may occur and the epidemiology of the disease, along with the potential role of novel biomarkers in disease recognition and classification.

Overview/Definition

In 2004, the Acute Dialysis Quality Initiative (ADQI), a consensus group of intensivists and nephrologists, proposed the Risk, Injury, Failure, Loss, and End-stage (RIFLE) classification system for AKI (Table 7.1) [1]. A major goal was to ensure that studies in the literature were comparable: because of differences in the definition of acute renal failure used in prior studies (e.g. ranging from a 0.5 mg/dl rise in creatinine to the need for renal replacement therapy [RRT]), the incidence and outcomes of AKI varied widely. That is, AKI defined as a 0.5 mg/dl increase in creatinine was much more common and associated with better outcomes than AKI defined as the need for RRT.

Importantly, the RIFLE criteria defined three levels of decreased kidney function (risk, injury, failure; Table 7.1) along with loss of kidney function (persistent AKI, defined as the need for RRT for 4 weeks) and end-stage renal disease. The rationale for defining different levels of disease severity was that earlier AKI recognition might allow for earlier treatment (including supportive care and nephrotoxin avoidance, for example), recognizing that there is an inherent tradeoff between sensitivity and specificity that may occur when small changes in serum creatinine are used to define AKI. In addition, the RIFLE criteria defined AKI using changes in either serum creatinine or urine output, with the rationale that these are both markers of decreased kidney function. However, it should be noted that studies prior to the development of the RIFLE criteria almost universally used serum creatinine, not urine output, to define acute renal failure. In addition, at the time the RIFLE criteria were published, the literature on the predictive value of graded reductions in urine output for adverse outcomes was limited, with no data to support the concept that the urine output criteria proposed were in any way "equivalent" to the creatinine-based AKI criteria. Subsequent studies have suggested that AKI defined by

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Table 7.1 Comparison of consensus AKI definitions.

Stage	Urine output (common to all three)	Creatinine (KDIGO)	Creatinine (AKIN)	RIFLE category	Creatinine (RIFLE)
1	<0.5 ml/kg/h for 6–12 h	1.5–1.9 times baseline over 7 days or ≥0.3 mg/dl absolute increase over 48 h	1.5–2 times baseline or ≥0.3 mg/dl absolute increase within 48 h	Risk	≥1.5 increase in SCr within 7 days, sustained for ≥24 h
2	<0.5 ml/kg/h for ≥12 h	2.0–2.9 times baseline	>2–3 times baseline	Injury	≥2 increase in SCr
3	<0.3 ml/kg/h for ≥24 h or anuria for ≥12 h	≥3.0 times baseline, or increase to ≥4.0 mg/dl or initiation of RRT	>3.0 times baseline, or increase to ≥4.0 mg/dl (with an increase of 0.5 mg/dl) or initiation of RRT	Failure	≥3.0 increase in SCr or increase to ≥4.0 mg/dl (with an increase of 0.5 mg/dl) or initiation of RRT
				Loss	Complete loss of kidney function >4 weeks
				End-stage kidney disease	End-stage renal disease >3 months

Urine output criteria are common to all three. The ADQI RIFLE definition incorporated three categories of injury and two outcomes that varied by severity. Outcomes were eliminated from the subsequent Acute Kidney Injury Network (AKIN) and KDIGO definitions. The AKIN definition incorporated smaller changes in SCr and the KDIGO definition added more definitive time frames to the definition.

urine output criteria is much more common than AKI defined by creatinine criteria. Isolated AKI by urine output criteria is generally associated with a significant increase in the risk of death compared to those with no AKI, but generally lower risk compared to those with isolated AKI by creatinine criteria; those with AKI by both urine output and creatinine criteria have the greatest risk of death [2–5]. However, despite these caveats, creating consensus criteria for both changes in serum creatinine and urine output to define AKI was a critical step to moving the field forward. Finally, the RIFLE criteria recognized that relative changes in serum creatinine are important, that is, in someone with normal kidney function (e.g. baseline creatinine of 0.8 mg/dl), an increase in serum creatinine to 1.6 mg/dl represents a larger change in renal function than a rise of the same absolute magnitude in an individual with underlying chronic kidney disease (e.g. a rise from 4.0 to 4.8 mg/dl). Therefore, inherent in the RIFLE criteria is knowledge of a baseline creatinine. In the absence of a baseline creatinine, the RIFLE criteria proposed the use of a creatinine that represents an estimated glomerular filtration rate (eGFR) of 75 ml/min/1.73 m^2 by the Modification of Diet in Renal Disease (MDRD) estimating equation (also referred to as MDRD-75).

Following a number of studies suggesting that small absolute changes in serum creatinine are also associated with an increased risk of adverse outcomes, the RIFLE criteria were modified slightly by the Acute Kidney Injury Network (AKIN) [6]. These studies included a large retrospective study by Chertow et al. [7], which demonstrated that a 0.3–0.4 mg/dl increase in serum creatinine was associated with a 1.7-fold higher odds of death in multivariable analysis adjusting for age, gender, chronic kidney disease, and diagnosis codes. Thus, a 0.3 mg/dl increase in serum creatinine over 48 hours was added to the definition of mild (Stage 1) AKI (see Table 7.1). Importantly, both "loss" and "end-stage kidney disease" were recognized to be outcomes of AKI and dropped from the definition.

In 2012, Kidney Disease Improving Global Outcomes (KDIGO) comprehensively reviewed the field of AKI to develop a series of consensus guidelines focused on AKI diagnosis and treatment [8]. As part of these guidelines, the RIFLE and AKIN criteria were combined into the KDIGO definition (Table 7.1). In addition, the concept of AKD was introduced. This comprises AKI, along with a decrease in eGFR <60 ml/min/1.73 m^2, decrease in glomerular filtration rate (GFR) by ≥35% or increase in serum creatinine (SCr) by >50% for less than 3 months. Subsequently, a staging system for AKD analogous to that for AKI has been proposed, though this definition has not been as well validated [9]. Along the same lines, criteria to define and stage kidney recovery have yet to be well standardized and are, when creatinine is used as the measure of kidney function, potentially confounded by changes in nutritional status and muscle mass (see below for additional discussion).

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Classification of AKI

Since at present the majority of care for AKI is supportive and focused on the underlying etiology (e.g. volume resuscitation for the patient with volume depletion and "prerenal" physiology), it is imperative to search for and identify the primary cause of AKI [10]. Careful history-taking, chart review, and physical examination remain the fundamental tenets of the workup. Specific causes of AKI that may warrant cause-specific therapy include acute interstitial nephritis (withdrawal of offending medication, steroids), vasculitis/acute glomerulonephritis (consideration of immunosuppression), thrombotic microangiopathy (consideration of pheresis or monoclonal antibody therapy targeting the complement pathway), and urinary tract obstruction (relief/decompression of obstruction).

Broadly speaking, AKI can be subdivided into prerenal, intrarenal, and postrenal etiologies (Table 7.2). Prerenal physiology refers to any cause of decreased kidney perfusion, which may be due to volume depletion itself. Alternatively, decreased kidney perfusion may occur due to other pathologic conditions, including heart failure, liver disease, nephrotic syndrome, and impaired venous return in the setting of abdominal compartment syndrome. Intrarenal failure may be due to damage to the vasculature, glomerulus, tubules, or interstitium. Finally, postrenal AKI is due to obstruction anywhere along the collecting system. In particular in those who have had a kidney transplant or who have a solitary kidney, it is essential to assess for and rule out obstruction. In hospitalized patients, the most common form of AKI is acute tubular necrosis (intrarenal) due to ischemia, nephrotoxins, or

Table 7.2 Classification of AKI by etiology.

Decreased renal perfusion, e.g. "prerenal" states	
Hypovolemia	Increased losses; poor oral intake
Reduced cardiac output	Heart failure, cardiac tamponade, massive pulmonary embolism
Renal vasomodulation/shunting	Medications (NSAIDs, ACE/ARB, cyclosporine, iodinated contrast), hypercalcemia, hepatorenal syndrome, abdominal compartment syndrome
Systemic vasodilation	Sepsis, hepatorenal syndrome
Intrarenal causes	
Vascular	Renal artery stenosis
Microvascular	Thrombotic microangiopathies, cholesterol emboli
Glomerular	Rapidly progressive (crescentic) glomerulonephritis
	Immune complex diseases: IgA nephropathy, post-infectious, lupus, mixed cryoglobuminemia with MPGN
	Pauci-immune glomerulonephritis: ANCA-associated and ANCA-negative
	Some causes of nephrotic range proteinuria may associate with AKI: in particular light-chain cast nephropathy
Tubulointerstitium	Acute interstitial nephritis: medications, infection, lymphoproliferative disease
	Pigment nephropathy: rhabdomyolysis (myoglobin), massive hemolysis (hemoglobin)
	Crystal nephropathy: uric acid (tumor lysis), acyclovir, sulfonamides, protease inhibitors (indinavir, atazanavir), methotrexate, ethylene glycol, acute phosphate nephropathy, oxalate nephropathy
	Myeloma-associated AKI (cast nephropathy)
	Acute tubular necrosis: ischemia (shock), medications
	Sepsis-associated AKI
Postrenal	
Bladder outlet	Benign prostatic hypertrophy, strictures, blood clots
Ureteral	Bilateral obstruction (or unilateral with one kidney): stones, malignancy, retroperitoneal fibrosis
Renal pelvis	Papillary necrosis (NSAIDs), stones

Etiologies of AKI can be broadly divided into prerenal, intrarenal, and postrenal causes and then further subdivided.

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sepsis. At present, the classification of AKI is based predominantly on history/clinical context and may be supported by laboratory testing. The laboratory studies will depend on the suspected etiology of AKI and may include a serologic workup for vasculitis or a peripheral blood smear to assess for hemolysis if thrombotic microangiopathy is suspected. Urinalysis and urine microscopy may be helpful. In particular, the presence of casts in the urine may provide insight into the cause of AKI (Table 7.3). However, casts are not required for these diagnoses. Urinalysis scores which quantify the number of renal tubular epithelial cells or cast elements per microscopic fields have been repeatedly shown to be specific for AKI and correlate with AKI severity (in this case, with acute tubular necrosis as the etiology of AKI) [11–13]. Widespread acceptance has been hampered by the lack of large-scale validation and the relatively modest sensitivity for urine microscopy for detecting AKI [11, 14–16]. Table 7.4 summarizes several of the published urinalysis risk scores.

Table 7.3 Overview of urine cast types with typical associations.

Waxy	Chronic kidney disease
Hyaline	Prerenal azotemia
Granular	Acute tubular necrosis
Dark/muddy brown	Acute tubular necrosis
White blood cells	Interstitial nephritis
Red blood cells	Glomerulonephritis

Table 7.4 Review of urine microscopy scoring systems for the diagnosis of AKI due to acute tubular necrosis.

Study	Scoring system
Chawla et al. [11]	Grade 1: No casts or RTE Grade 2: At least 1 cast or RTE but <10% of LPF Grade 3: Many casts or RTEs (between 10% and 90% of LPF) Grade 4: Sheet of muddy brown casts and RTEs in >90% of LPF
Perazella et al. [12]	0 points: No casts or RTE seen 1 point each: 1–5 casts per LPF or 1–5 RTEs per HPF 2 points each: ≥6 casts per LPF or ≥6 RTEs per HPF
Bagshaw et al. [14]	0 points: No casts or RTE seen 1 point each: 1 casts or 1 RTEs per HPF 2 points each: 2–4 casts or RTEs per HPF 3 points each: ≥5 casts or ≥5 RTEs per HPF

RTE, renal tubule epithelial cells; LPF, low power field; HPF, high power field.

Limitations of SCr to Define AKI

With regards to defining AKI itself, in individuals with limited muscle mass (e.g. older adults, those with end-stage liver disease), SCr may overestimate eGFR because it is a breakdown product of creatine derived from muscle. Across the world, SCr measurements are now harmonized to IDMS standard materials, so there is not much variation in the laboratory measurement of serum creatinine. However, at high levels, chromogens, both endogenous and exogenous (e.g. bilirubin, uric acid, ascorbic acid, some cephalosporins, and ketones), may interfere with the creatinine assay [8]. Thus, there has been tremendous interest in identifying other endogenous filtration markers (e.g. functional markers) that are not associated with muscle mass to define chronic kidney disease (e.g. cystatin C [17]). However, changes in markers including cystatin C have not been as well-studied in the context of AKI, so there is no consensus regarding absolute biomarker levels or changes in biomarker levels that could be used to define AKI. Finally, there is growing interest in other filtration markers, including proenkephalin [18], but more studies are needed.

Biomarkers of AKI/AKD

While there have been numerous publications on the role of novel biomarkers in the risk stratification, diagnosis, prognosis, and long-term outcomes of AKI, to date there has not been the formal inclusion of these novel tests into diagnostic criteria and none have gained wide clinical acceptance. Regardless, these investigations have helped to focus the ideal characteristics of a novel biomarker specific for AKI/AKD. Such biomarkers should (i) be organ specific and allow differentiation between the traditional causes of AKI (intrarenal, prerenal, and postrenal), (ii) detect AKI early in the course and predict the course/future implications of AKD, (iii) identify the source/nature of AKI, (iv) be site-specific and able to inform pathologic changes in various segments of renal tubules and correlate with the histology on kidney biopsies, and (v) be easily and reliably measured in a noninvasive, rapid manner, which implies that the marker is stable in its matrix and relatively inexpensive to measure.

The concept of functional versus damage markers of kidney injury is similar to diagnostic models from other aspects of medical care. It is common to see functional biomarkers (e.g. electrocardiograms or imaged-based stress tests) paired with damage biomarkers (creatine kinase, troponins). An ADQI consensus statement recommended that the combination of functional and damage biomarkers

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would be helpful to define AKI. (Figure 7.1) [19]. By stratifying patients across these two domains, a novel cohort with "subclinical AKI" can be identified: those with a change in damage biomarkers in the absence of change in functional biomarkers [20, 21]. This group of patients, who would not be detected by creatinine or urine output-based KDIGO criteria, appears to have the same risk for severe AKI and adverse outcomes (e.g. inpatient mortality) as patients who have a change in functional markers in the absence of change in damage biomarkers (more traditionally thought of as having prerenal azotemia). In a pooled, prospective observational cohort of 2322 subjects (1452 with cardiac surgery and 870 with critical illness), Haase et al. designated subjects as neutrophil gelatinase associated lipocalin (NGAL)-positive or NGAL-negative and creatinine-positive or creatinine-negative. They demonstrated that individuals who were NGAL-positive/creatinine-negative needed RRT more than 16 times more frequently than those who were NGAL-negative/creatinine-negative (odds ratio 16.4, 95% confidence interval 3.6–76.9) [20]. NGAL-positive/creatinine-negative patients were also in ICU and hospital longer and more likely to experience inpatient mortality compared to NGAL-negative/creatinine-negative subjects. The incidence and duration of these outcomes were similar in the NGAL-positive/creatinine-negative and NGAL-negative/creatinine-positive cohorts. This concept of damage biomarker positive/functional biomarker negative patients being at increased risk for adverse outcomes has been validated in other cohorts [22, 23].

In 2014, the combination of urine tissue inhibitor of metalloproteinase-2 and insulin-like growth factor binding protein-7 (TIMP2*IGFBP7) became the first novel AKI biomarker approved by the Food and Drug Administration (FDA). The intended use of TIMP-2*IGFBP7 is to assess the risk of developing KDIGO Stage 2 AKI over the next 12 hours in high-risk critically ill patients [24, 25]. Some studies have shown improved outcomes when supportive care bundles are applied to patients identified by high levels of TIMP-2*IGFBP7 [26, 27], but TIMP-2*IGFBP7 has not yet gained widespread acceptance. In other parts of the world (e.g. Europe and Japan, respectively), urinary NGAL and liver-fatty acid binding protein (L-FABP) can be measured in clinical practice as measures of AKI, though clear thresholds for AKI have not been developed.

As previously mentioned, there has been extensive investigation into several biomarkers of kidney injury in several

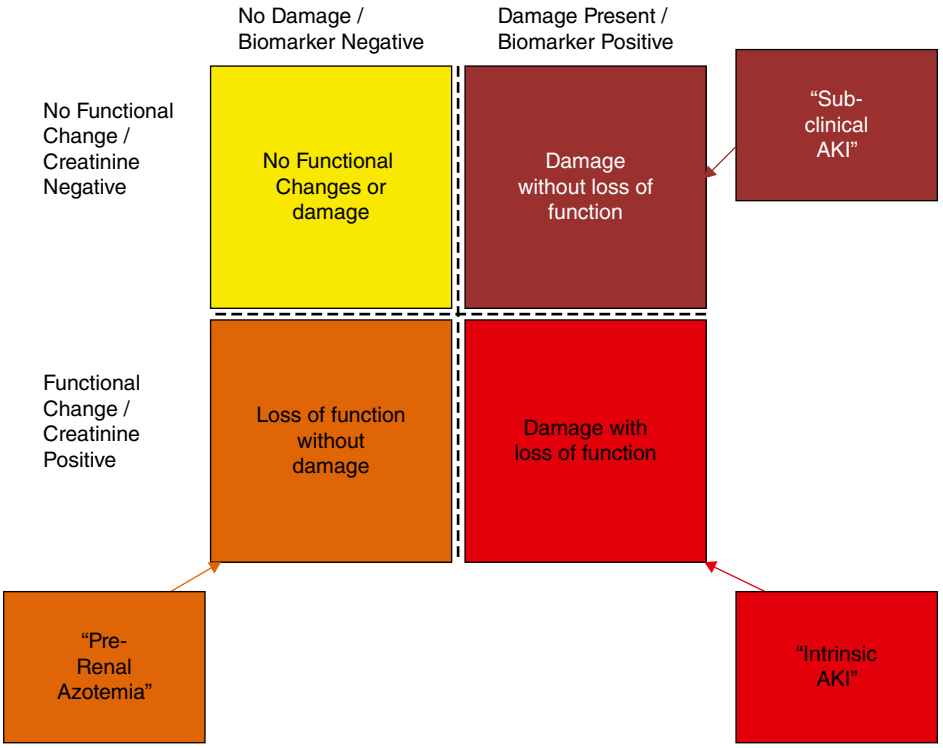

Figure 7.1 The Acute Dialysis Quality Initiative recommended criteria for defining acute kidney injury (AKI) in terms of changes in biomarkers of kidney function (SCr) and biomarkers of kidney damage/injury. This paradigm allows for the combination of injury biomarkers with SCr and has proven useful in the discrimination of patients with AKI and resulted in the concept of "subclinical AKI." *Source:* Adapted from [19].

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clinical settings, including after cardiac surgery, critical illness/ICU admission, or admission to the emergency department. In each of these settings biomarkers have been examined to determine their association with a variety of short and long-term outcomes, including but not limited to the early detection of AKI, the temporal nature of the AKI (transient versus persistent), the detection of severe (e.g. dialysis requiring) AKI, and inpatient mortality. It should not be surprising that a single biomarker has not been associated with all of these outcomes across multiple settings, given the biological heterogeneity that underlies the diverse etiologies of AKI. However, this does not diminish the importance of their performance for individual endpoints in specific clinical settings. Table 7.5 summarizes the current state of the ability of biomarkers to detect clinical endpoints related to AKI in a variety of settings. We anticipate continued investigation of these biomarkers as well as novel tests over the course of the next decade.

Epidemiology of AKI: Identification of High-risk Patients

In terms of identification of high-risk patients, both chronic kidney disease and the presence of proteinuria/albuminuria (as dip-stick, protein to creatinine ratio or albumin to creatinine ratio) have been strongly implicated as risk factors for AKI [29–31]. However, in particular in the perioperative setting, preoperative risk stratification, while helpful, does not necessarily robustly predict postoperative AKI because AKI typically is due to a complicated operative course in a high-risk patient. For example, in a classic analysis, using data from more than 33 000 patients at the Cleveland Clinic, a scoring system to identify those at high risk of dialysis requiring AKI was developed, with a robust area under the curve of 0.81 and 0.82 in the test and validation datasets, respectively [32]. However, given the very large size of the low risk group, more dialysis events occurred in the lower risk groups than the highest risk group. Thus, while such scores may be useful for preoperative risk assessment and for enrichment of populations for clinical trials, they are of somewhat limited utility because they typically do not incorporate risk based on the ongoing clinical course/current situation.

Thus, there has been significant interest in risk stratification to identify patients who may benefit from novel/damage biomarker assessment. For example, the urine output following a protocolized intravenous dose of furosemide in the setting of stage 1 or 2 AKI (furosemide stress test, FST) has been shown to reliably predict AKI progression to Stage 3 and the need for RRT [33–35]. As a functional biomarker of proximal tubule and loop of Henle function, the FST has outperformed several damage biomarkers when compared directly [33, 36]. With the renal angina index, patient demographics and other risk factors (comorbidities, procedure/medication exposure) are combined with small changes in serum creatinine and/or urine output and the presence of volume overload to identify patients where damage biomarkers should be measured and may identify those with early AKI or at high risk of AKI [37]. Multiple novel risk scores (some of which include AKI biomarkers) have also been proposed [38, 39]. However, to date no single risk score (or biomarker) has been universally validated.

In addition to this explosion of more traditional risk scores, there is increasing interest in developing complex risk assessment models which can utilize all of the information that is available in the medical record to identify patients at risk for AKI [40–43]. The appeal of such risk assessment models is that they can incorporate the most up-to-date data to evaluate changes in risk. While such electronic biomarkers of AKI represent a potential future option, they will require wide-scale validation prior to becoming part of the standard of care. In the near future, electronic risk scores and biochemical biomarkers (in particular, damage biomarkers) are likely to be incorporated in AKI/AKD definitions.

Epidemiology of AKI: Incidence and Outcomes

The exact incidence and outcomes of AKI will vary depending on the definition used and clinical setting. For example, more severe AKI requiring dialysis in sicker patients (e.g. ICU patients) is associated with a greater risk of death than stage 1 KDIGO AKI in all hospitalized patients. Although AKI has long been recognized to associate with a high risk of short-term adverse outcomes such as death, more recently it has become clear that AKI is associated with an increased risk of a number of long-term adverse outcomes [44, 45], including de novo chronic kidney disease/chronic kidney disease progression, cardiovascular disease, and death. Again, these associations are likely graded, with greater risk associated with more severe AKI. That said, even fully recovered AKI (based on serum creatinine) appears to be associated with an increased risk of adverse outcomes, including chronic kidney disease and death [46]. Thus, in AKI survivors, clinicians should be aware of the increased risk of long-term adverse outcomes.

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Table 7.5 Biomarker performance in detecting AKI from multicenter studies at a variety of clinical timepoints.

	Perioperative AKI				Critically ill			Emergency room	
	Preoperative AKI risk	Early postoperative AKI	AKI progression	Long-term mortality	Early diagnosis of AKI	Type of AKI (transient vs. intrinsic)	Need for RRT	Early diagnosis of AKI	Type of AKI (transient vs. intrinsic)
Urine NGAL	N/A	+	−	+	+	+	+	+	+
Blood NGAL	−	+	+	+	−	?	−	?	?
Blood CysC	+	+	−	?	+	+	+	?	?
Urine CysC	N/A	−	−	−	+	+	+	+	+
Proenkephalin	?	?	?	?	+	+	+	?	?
Urine IL-18	N/A	+	+	+	+	+	+	+	+
Urine KIM-1	N/A	+	−	+	+	−	−	+	+
Urine L-FABP	N/A	−	−	+	?	?	−	+	+
TIMP-2 IGFBP-7	N/A	+	+	+	+	?	+	+	?
Urine protein/albumin	+	+	+	+	?	?	?	?	?

NGAL, neutrophil gelatinase associated lipocalin; CysC, cystatin C; IL-18, interleukin-18; KIM-1, kidney injury molecule-1; L-FABP, liver fatty acid binding protein; TIMP-2 IGFBP-7, tissue injury metalloprotease 2 insulin-like growth factor binding protein-7.
+, data published displays the ability to detect this aspect of AKI.
−, data published does not display the ability to detect this aspect of AKI.
?, no large multicenter data published on this biomarker/aspect of AKI.
N/A, not applicable either because (a) biomarkers of tubular injury have no role in preoperative risk screening or (b) serum creatinine is intrinsic to the definitions of AKI being tested.
Source: Adapted and expanded from Koyner and Parikh et al. [28]

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8

Prerenal Failure and Obstructive Disease

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Introduction

Prerenal azotemia is the most common form of acute kidney injury (AKI) in hospitalized patients and, if uncorrected, can lead to ischemic parenchymal damage and acute tubular necrosis (ATN) [1, 2]. The clinical syndrome of prerenal failure is characterized by intact tubular function with impaired filtration function because of renal hypoperfusion and usually manifests as low urine volume, reduced urinary concentration of sodium (UNa) and fractional excretion of sodium (FeNa%), and an elevated ratio of blood urea nitrogen to serum creatinine (Cr).

Prerenal failure is the result of either true volume depletion, as occurs with hemorrhage or excessive diuresis, or "effective" volume depletion in circumstances such as congestive heart failure (cardiorenal syndrome), liver failure with ascites (hepatorenal syndrome), and sepsis. The etiologies for prerenal failure are outlined in Table 8.1. In both instances decreased intravascular volume causes baroreceptor stimulation and enhanced adrenergic output, leading to systemic and local regulatory mechanisms aimed at restoring normal perfusion pressure.

At the level of the kidney, a complex interplay between neuroendocrine and vasoactive agents initially compensates for decreased perfusion pressure. Specifically, angiotensin II causes preferential vasoconstriction of the efferent arteriole, increased proximal tubular reabsorption, elevation of glomerular hydrostatic pressure, and a reduced glomerular ultrafiltration coefficient. Because of angiotensin II preferential constriction of the efferent arteriole, with mild to moderate volume depletion, the glomerular filtration rate (GFR) is maintained. With severe volume depletion, frank ischemic ATN may ensue. Since the GFR in such situations is dependent on relative efferent arteriolar vasoconstriction, the use of angiotensin II antagonists, such as angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs), can precipitate ATN. The vasoconstrictor effects of angiotensin II are opposed by endogenously produced prostaglandins and nitric oxide. When used acutely in prerenal failure, nonsteroidal anti-inflammatory drugs lead to unopposed vasoconstriction and worsening of renal function.

The differential vasoconstrictor activity of AII between the afferent and efferent arteriole may be best explained by the interaction of AII-mediated vasoconstriction with various local mediators of vasodilation stimulated by AII. This is illustrated by contrasting results between *in vivo* and *in vitro* vasoconstrictor studies. Microperfusion studies have demonstrated a 100-fold greater sensitivity for AII to elicit a vasoconstrictor response in the efferent versus afferent arteriole. In vitro studies, however, failed to show a difference in vasoconstrictor sensitivity in these vascular beds, suggesting that the production of other local factors stimulated by AII may contribute to the differential response. These include prostaglandins secreted by the glomerulus in response to AII. Experimental inhibition of prostaglandin synthesis with indomethacin enhances afferent and efferent arteriole vasoconstriction by AII, with afferent arteriolar response to AII increasing tenfold [3].

In response to decreased renal perfusion, activation of the renin–aldosterone axis and release of antidiuretic hormone also occur, increasing sodium and water retention in an attempt to restore intravascular volume. These temporizing physiologic measures are necessary to maintain perfusion pressures in the face of frank volume depletion but are ineffective in sepsis and clearly deleterious in conditions such as heart failure with pulmonary edema.

Given this background, prerenal failure is not a simple case of hypovolemia that can be corrected by administration

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Table 8.1 Causes of prerenal failure.

Decreased cardiac output	Redistribution/vasodilation
Myocardial infarction	Cirrhosis
Congestive heart failure	Nephrotic syndrome
Pericardial tamponade	Pancreatitis
Positive pressure ventilation	Sepsis
Pulmonary embolism	Crush injuries
	Intestinal obstruction
Hypovolemia	*Vascular disease*
Hemorrhage	Renal artery stenosis
Diuresis	Atheroembolism
Diarrhea	Vasculitis
Excessive sweating	Aortic aneurysm dissection

of intravascular crystalloid or colloid. Treatment must, by necessity, be directed at the underlying pathophysiology that has triggered the compensatory physiologic response common to all etiologies. Therefore, an evidence-based approach to the treatment of prerenal azotemia requires a review of the available data on several subgroups of patients and cannot take a "one size fits all" approach.

Diagnosis

Many causes of prerenal failure are clinically obvious. With reliance on history, physical examination, and certain laboratory findings, patients with true volume depletion are often easily identified and can be treated with aggressive volume repletion. Such patients demonstrate orthostatic hypotension, tachycardia, dry mucous membranes, low urinary output, and poor skin turgor. Other patients require a more careful evaluation for fluid responsiveness. Accurate predictors of fluid responsiveness are essential in the management of hemodynamic instability. For those who are fluid responsive, they guide fluid replacement. For those who are not, they guide vasopressor and inotrope use and help avoid the detrimental effects of excess fluid. Pulse pressure variation (PPV) may be measured in the mechanically ventilated patient and is derived from the arterial waveform. It is defined as the maximum pulse pressure in a respiratory cycle minus the minimum pulse pressure divided by the mean of these two values [$PPV = 100 \times (PP_{max} - PP_{min})/PP_{mean}$] In a systematic review to determine the ability of dynamic changes in arterial waveform-derived variables, such as PPV, to predict fluid responsiveness and compare these with static indices of fluid responsiveness, dynamic changes of arterial waveform-derived variables during mechanical ventilation were highly accurate in predicting volume responsiveness in critically ill patients when compared with traditional static indices of volume responsiveness, such as CVP [4]. In non-ventilated patients, the passive leg raise (PLR) has been shown to be predictive of a response to a fluid challenge. In this maneuver, the patient is passively moved from a 45-degree semi-recumbent position to supine with legs raised and held to 45 degrees for one minute. Baseline measurement (e.g., cardiac output) is obtained before the maneuver and repeated afterward. In a prospective, observational study, Duus, et al investigated the reproducibility of PLR vs fluid bolus using non-invasive cardiac output monitor (NICOM) for assessment of fluid responsiveness in spontaneously breathing ED patients. They enrolled 109 patients and each patient received two PLR and two boluses. PLR was strongly correlated with fluid responsiveness as measured by NICOM, whereas the boluses were less strongly correlated. In addition, PLR technique was more reproducible than the fluid bolus technique [5]. POCUS has also been used increasingly in recent years. One such use to assess volume status is IVC measurements. In a systematic review and meta-analysis, Orso, et al reviewed 26 studies that investigated the role of IVC collapsibility or distensibility or IVC diameter in critically ill patients (both ventilated and non-ventilated). Ultimately, they found that ultrasound evaluation of the diameter of the IVC and its respiratory variations was not a reliable method to predict fluid responsiveness [6]. Although much has been made of the utility of urinary indices in AKI (vide infra), they are unnecessary in such situations, and patients promptly respond to volume resuscitation.

CVP and PAOP

Although physicians often rely on central venous pressure (CVP) and pulmonary artery occlusion pressure (PAOP) to guide fluid administration to determine whether or not a patient has true volume depletion, there is little evidence that such measurements are clinically useful. There are no trials that have assessed the utility of these measurements specifically for determining the reversibility of prerenal failure.

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The CVP and PAOP are frequently used as means of determining cardiac preload and volume status. However, their use has been criticized because of poor ability to predict which patients will have improvement in their hemodynamic status when given fluid resuscitation [7]. As reviewed by Michard and Teboul, in three of five trials assessing the ability of CVP to predict fluid responsiveness in critically ill patients, defined as an improvement in either stroke volume or cardiac output, there was no significant difference in the baseline CVP measurements between responders and nonresponders. The two remaining studies reported lower baseline values of CVP in responders; however, the marked overlap of individual CVP levels did not allow for the identification of a discriminatory cutoff value. Likewise, baseline PAOP was not significantly lower in responders versus nonresponders in seven of nine studies. Three studies reported a significant difference in the baseline PAOP between the groups, being higher in responders in a single study and lower in responders in two studies. However, in none of the studies could a cutoff PAOP value be found that predicted the hemodynamic response to volume expansion. In normal subjects, Kumar and associates demonstrated a lack of correlation between initial CVP and PAOP values, and both end diastolic volume and stroke volume [8]. Furthermore, changes in both parameters following 31 of saline infusion did not correlate with changes in end diastolic volume and cardiac performance.

In addition, numerous randomized controlled trials (RCTs) and meta-analyses assessing the benefit of pulmonary artery catheters (PAC) in a variety of clinical circumstances have been reported [9–11]. In a meta-analysis of 13 RCTs, the use of PAC neither increased overall mortality and hospital days nor conferred any benefit [12]. Likewise, in an RCT of 676 patients with shock mainly from sepsis, ARDS, or both, early use of PAC did not significantly affect mortality or morbidity, including the need for dialysis [13]. Therefore, in critically ill patients with multiple reasons for prerenal failure (sepsis, capillary leak with third spacing, positive pressure ventilation, hypoalbuminemia, cardiac dysfunction, and liver disease), measurement of CVP and/or PAOP does not improve outcome and has poor predictive value for improvement in renal function.

Urine Output

The development of oliguria (urine output of less than 400 ml/day) does not ensure the presence of prerenal failure. It occurs in both prerenal failure states and numerous other causes of AKI, including ATN, obstructive nephropathy, glomerulonephritis, and atheroembolic disease. Despite the compensatory mechanisms invoked in response to decreased renal perfusion that increase salt and water retention by the kidneys in prerenal failure states, higher urine outputs can ensue in the face of underlying chronic kidney disease, salt wasting states such as adrenal insufficiency and cerebral salt wasting, concomitant use of diuretics, osmotic diuresis, and the presence of nonreabsorbed anions, such as ketones and bicarbonate in the urine.

Urinalysis

Urinalysis is often used to differentiate various causes of AKI. In prerenal failure, the urine is concentrated and the urinary sediment is bland. Bland urinary sediment, however, does not allow for discrimination between true and effective volume depletion. Furthermore, patients with prerenal failure can have abnormal sediment if they have a pre-existing renal disorder, bilirubin in the urine (causing granular casts), or microscopic hematuria and bacteruria from an indwelling bladder catheter. The utility of the urinalysis in differentiating prerenal failure from AKI has been called further into question by the results of two recent systematic reviews on the urinary findings in sepsis-related AKI (human and experimental animal studies). These systematic reviews demonstrated substantial heterogeneity between studies and suggested that the scientific basis for the use of urinary microscopy in septic AKI and, by extension, to differentiating ATN from prerenal failure is weak [14, 15].

On the other hand, Varghese, et al, showed in a recent prospective study that serial microscopic examinations of the urinary sediment revealed diagnostic findings of ATI otherwise not identified in a single examination [16]. This study used two different urinary cast scores developed by Chawla and Parazella, each of which has been previously validated to predict renal outcomes in AKI [17] and [18]. With Chawla's cast scoring index, there was a 99.8% interobserver agreement among three nephrologists who independently scored 30 patients with AKI due to ATI. In addition, the ROC AUC curve for the scoring index to predict renal recovery was 0.79, indicating that the scoring index may be useful in predicting renal outcomes. Parazella's scoring system was significantly associated with increased risk of worsening AKI (adjusted relative risk: 7.3; 95% confidence interval: 4.5 to 9.7 for worsening with score of > or =3 versus score of 0) and was more predictive than AKI Network stage at the time of consultation.

Urinary Indices

The measurement of urinary sodium (UNa) and calculation of the fractional excretion of sodium (FeNa%) has been routinely recommended as a means to differentiate oliguric prerenal failure from oliguric ATN, as shown in Table 8.2. In the sentinel study reported by Miller et al., a UNa concentration of less than 20 mEq/l had an 80% sensitivity and specificity for differentiating prerenal failure from ATN in the face of oliguria [19]. The FeNa% performed even better, with sensitivity and specificity of 98% and 95%, respectively. The utility of either measurement was significantly less in the absence of oliguria. However, there are numerous exceptions to the general rule [20–22]. Both UNa and FeNa% can be low, suggestive of prerenal failure with AKI from rhabdomyolysis, radiocontrast nephropathy, acute glomerulonephritis, multiple myeloma, amphotericin B toxicity, and early

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Table 8.2 Urinary indices in ARF.

	Number of patients with condition/total number of patients		
Index and range	**Prerenal failure**	**Oliguric ATN**	**Nonoliguric ATN**
Urine Na (mEq/l)			
<20	18/30 (60%)	0/24 (0%)	2/13 (6%)
20–40	12/30 (40%)	14/24 (59%)	11/31 (35%)
>40	0/30 (0%)	10/24 (41%)	18/31 (59%)
FeNa%			
<1	27/30 (90%)	1/24 (4%)	4/31 (12%)

Source: Adapted from Miller et al. [19].

obstructive nephropathy. Thus, the finding of renal sodium avidity does not allow one to discriminate between true and effective volume depletion nor reliably predict reversibility with volume administration.

Despite these limitations, a recent study demonstrates a potential role for FENa% in patients with cirrhosis. In a prospective analysis of 200 patients with decompensated cirrhosis with AKI, Gowda, et al evaluated the diagnostic utility of FeNa% and fractional excretion of urea nitrogen (FEUN%) for differentiating AKI phenotypes (i.e., prerenal, ATN, and HRS). After determining the optimal cutoffs, they validated their findings in an independent cohort of 50 patients. The AUC for FENa% was 86.6% and for FEUN% was 60.3% for ATN vs non-ATN. The AUC for FENa% to differentiate between HRS and non-HRS was 74.5%. FEUN% could not differentiate HRS vs non-HRS satisfactorily (60.4%). FENa% and FEUN% were unable to differentiate between prerenal and HRS (AUC < 70). Thus, among cirrhotics, FENa% at admission can be used to differentiate ATN from prerenal and HRS.

The use of diuretics can increase urinary sodium loss even in the face of prerenal failure, thus negating the utility of the FeNa%. Since the (FeUN%) is primarily dependent on passive forces, it is less influenced by the administration of diuretics and may be useful in the evaluation of AKI. A group of 102 patients with AKI was divided into three subgroups: prerenal failure, prerenal failure treated with diuretics, and ATN. The FeNa% was low in 92% of the prerenal failure group and 48% of prerenal failure patients receiving diuretics. Both groups had similar and significantly lower FeUN% values than the ATN patients [23].

Treatment

In the patient with clinically obvious volume depletion, adequate fluid resuscitation can be achieved by the administration of crystalloids, such as normal saline or lactated Ringers solution. Such patients often show remarkable improvement in their renal function over a short period of time.

In the complex or critically ill patient, the situation is more challenging. In this population, it is difficult to accurately determine intravascular volume and whether the prerenal failure is due to true or effective volume depletion, while concern is great for the potential harm of indiscriminant fluid administration in the face of acute lung injury or frank ARDS. There is also debate on what type of fluid, colloid versus crystalloid, is best for volume resuscitation in such patients. Although not specifically done to address prerenal failure, review of recent clinical trials in these areas can provide some type of general guideline.

Goal-directed Hemodynamic Management and Fluid Therapy

Previous observational nonrandomized studies have shown that patients who survived critical illness had higher values for cardiac index and oxygen delivery than those who died and that those values were higher than normal physiologic levels [26, 27]. Two studies of surgical patients showed significant decreases in mortality associated with therapy directed at increasing hemodynamic parameters to supraphysiologic values, whereas no benefit was seen in patients with sepsis and mixed groups of critically ill patients [28–31]. Subsequently, two RCTs assessed the benefit of goal-directed hemodynamic therapy in critically ill patients. In one trial of 100 patients randomized to dobutamine or placebo there were no differences in mean arterial pressure (MAP) or oxygen consumption despite higher cardiac index and oxygen delivery in the treatment group [32]. In fact, the treatment group had a significantly higher mortality rate than the placebo group. In another trial of 762 patients randomized into one of three intervention groups, hemodynamic therapy aimed at achieving supranormal values for cardiac index or normal values for mixed venous oxygenation saturation did not reduce morbidity or mortality [33].

In 2001, Rivers et al reported the results of a nRCT on early goal-directed therapy (EGDT) in the treatment of severe sepsis and septic shock [34]. Patients with severe sepsis or septic shock were randomly assigned upon emergency center arrival to either 6 hours of EGDT or standard therapy prior to admission to the ICU. Active intervention aimed at achieving a central venous oxygen saturation of 70% included saline boluses targeted to a CVP level of

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8–12 mmHg, vasopressor agents to maintain a MAP greater than 65 mmHg, transfusion to a hematocrit of 30%, and dobutamine. Although the patients assigned to active intervention received more fluid and blood products in the initial 24-hour period, they experienced a significantly reduced rate of organ failure and death.

Subsequently, the ARDS Clinical Trials Network assessed optimal fluid management in patients in the ICU with acute lung injury [4]. In this RCT, 1000 patients were assigned to either a conservative or liberal strategy of fluid management using explicit protocols applied for 7 days. The mean cumulative fluid balances in the conservative versus liberal groups were −136 and 6992 ml, respectively. Although there was no difference in mortality, the conservative group had significantly reduced ventilator and ICU days, and improved oxygenation. Importantly, conservative fluid management did not increase the need for renal replacement therapy (RRT). Three independent multicenter RCTs evaluated EGDT [24]. All three trials confirmed that there was no survival benefit compared to usual resuscitation. In a patient level meta-analysis from these trial, EGDT did not result in better outcomes than usual care and was associated with higher hospitalization costs across a broad range of patient and hospital characteristics [25].

Crystalloid Versus Colloid Fluids

The putative superiority of colloid over crystalloid fluids in the resuscitation of the critically ill patient has been a source of considerable controversy. Aggressive hydration with crystalloid solutions such as normal saline can worsen interstitial edema and pulmonary function. Colloidal solutions, such as various starches and human albumin, might appear to be attractive alternatives, but there is little solid evidence of their superiority in clinical trials. Systematic reviews of RCTs comparing crystalloids with colloids have yielded conflicting results. Some trials have found an increased mortality rate associated with the administration of human albumin and hydroxyethylstarch, while others have not [35–38]. More recently, a large, randomized, controlled prospective trial of albumin versus saline in almost 7000 critically ill patients found no benefit of one over the other [39]. Specifically, there was no demonstrable effect on mortality, renal function, or the frequency of RRT. Of note, patients with cirrhosis were excluded from this trial, and limited data suggest that albumin is useful to prevent AKI in cirrhotic patients with spontaneous bacterial peritonitis [40].

In a systematic review and meta-analysis that evaluated hemodynamic response to crystalloids/colloids in critically ill adults, central venous pressure was significantly lower with crystalloids vs. albumin (mean difference [MD]: −3.5 mm Hg; $p = .03$) or gelatin (MD: −9.2 mm Hg; $p = .02$). Compared with the albumin group, cardiac index was significantly lower in the crystalloid group (MD: −0.6 L/min/m^2, $p < .001$). All mortality and 90-day mortality were significantly lower for crystalloids compared with HES (relative risk 0.91; $p = .009$ and 0.9; $p = .005$, respectively). These findings suggest that crystalloids are less effective than colloids at hemodynamic stabilization in this population [41]. In a recent Cochrane review assessing the effect of using colloids vs crystalloids in critically ill patients on mortality and need for blood transfusion or renal replacement therapy (RRT), using various colloids vs crystalloids appeared to make little or no difference to mortality. Starches probably slightly increase the need for blood transfusion and RRT [42].

High- chloride Versus Balanced Fluids

Recent attention has shifted toward the potential negative effects of chloride in intravenous fluids on patient outcomes. The concentration of chloride in human plasma is approximately 100 meq/l. In 0.9% saline, it is much higher at 154 meq/l. In Ringer's lactate (LR), it is still somewhat elevated at 109 meq/l, and in Plasma-Lyte, it is more physiologic at 98 meq/l.

Two recent studies from a single center investigated whether fluid resuscitation of noncritically ill (SALT-ED) and critically ill (SMART) patients with balanced crystalloid vs isotonic crystalloid in the emergency department resulted in earlier hospital discharge. The primary outcome was hospital-free days (days alive after discharge before day 28) and the secondary outcome included a composite of major adverse kidney events within 30 days. The type of crystalloid (balanced vs isotonic) administered in the emergency department was assigned to each patient on the basis of calendar month, with the entire emergency department crossing over between balanced crystalloids (mostly lactated ringers) and saline monthly during the 16-month trial. Results showed that the number of hospital-free days did not differ between the balanced crystalloids and saline groups (median, 25 days in each group; adjusted odds ratio with balanced crystalloids, 0.98; 95% confidence interval [CI], 0.92 to 1.04; $P = 0.41$). However, balanced crystalloids resulted in a lower incidence of major adverse kidney events within 30 days than saline (4.7% vs. 5.6%; adjusted odds ratio, 0.82; 95% CI, 0.70 to 0.95; $P = 0.01$) [43]. In the SMART trial, critically patients were assigned to receive saline or balanced crystalloids in a randomized fashion. The primary outcome was a major adverse kidney event within 30 days—a composite of death from any cause, new renal replacement therapy, or persistent renal dysfunction—or 30 days, whichever occurred first. Among the 7942 patients in the balanced-crystalloids group, 1139 (14.3%) had a major adverse kidney event, as compared with 1211 of 7860 patients (15.4%) in the saline group (marginal odds ratio, 0.91; 95% confidence interval [CI], 0.84 to 0.99; conditional odds ratio, 0.90; 95% CI, 0.82 to 0.99; $P = 0.04$). In-hospital mortality at 30 days was 10.3% in the balanced-crystalloids group and 11.1% in the saline group ($P = 0.06$). The incidence of new renal-replacement therapy was 2.5% and 2.9%, respectively ($P = 0.08$), and the incidence of

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persistent renal dysfunction was 6.4% and 6.6%, respectively (P = 0.60). The authors concluded that in critically ill adults, the use of balanced crystalloids for IV resuscitation resulted in a lower rate of the composite outcome of death from any cause, new renal-replacement therapy, or persistent renal dysfunction than the use of saline. [44].

Summary

In the complex medical patient, prerenal failure can occur from either true or effective volume depletion. Since both circumstances share the same physiologic derangements, clinical parameters such as urine output and urinary electrolytes do not have any discriminatory power between the two. It is also difficult to predict which patients will benefit from volume resuscitation based on measurement of the CVP or PAOP. Often, the only way to determine if the renal failure is reversible is to provide an empiric "fluid challenge" and assess the clinical response. With regard to approaching the critically ill patient who may be functionally prerenal failure, fluid management is dependent on timing. Early intervention with goal-directed therapy, resulting in a positive fluid balance in the first 24 hours, is associated with reduced organ failure. In patients already in the ICU with lung injury, a conservative fluid approach improves pulmonary function without adverse renal effects.

Cardiorenal Syndrome

A recent classification of CRS proposed by the 7th Acute Dialysis Quality Initiate consensus conference has divided the syndromes into those that are "cardiorenal" referring to when cardiac dysfunction leads to kidney dysfunction and those that are "renocardiac" referring to when primary kidney dysfunction leads to cardiac dysfunction. These syndromes are further classified based on their acuity and the presence of a systemic (non-cardiac, non-renal) illness that may play a role in the pathophysiology [45]. There are 4 major mechanisms implicated in CRS: increased renal venous pressure (ie, venous congestion), neurohumoral imbalances, reduced renal perfusion, and right ventricular dilation and dysfunction [46].

Venous hypertension is thought to result in decreased renal perfusion, raised kidney interstitial pressure, narrowed arterial-to-venous renal pressure gradient, decreased glomerular filtration rate (GFR), maladaptive autoregulatory responses, and other characteristic neurohumoral imbalances. This higher renal venous pressure attenuates glomerular filtration, causes tubule collapse, and may trigger tubulointerstitial fibrosis [46]. (The neurohumoral mechanisms underlying CRS consist of activation of the renin-angiotensin-aldosterone and sympathetic nervous systems as well as increased production of antidiuretic hormone and endothelin 1. These processes increase salt and water retention and systemic vasoconstriction, which in turn decrease renal perfusion. Activation of the previously mentioned systems overrides the vasodilatory effects of natriuretic peptides, nitric oxide, prostaglandins, and bradykinin. Chronic and acute exacerbations of CHF are associated with widespread inflammation and high levels of proinflammatory cytokines, which may further boost cardiac, kidney, and other tissue dysfunction [46].

Renal perfusion is regulated by adenosine receptors involved with tubuloglomerular feedback (TGF) signaling, and maintain intrarenal vascular tone via a number of pathways which, in CRS, result in afferent arteriolar vasoconstriction and efferent arteriolar dilation. Actions of adenosine at the macula densa and mesangium depend on angiotensin, renin, nitric oxide, and prostaglandin levels, which are altered in CRS [46].

Right ventricular dysfunction increases central venous pressure, which in turn increases renal venous pressure. Right ventricular dilation and dysfunction also reduce left ventricular filling and decrease renal arterial pressure. The combination of increased renal venous and decreased renal arterial pressures diminishes the pressure gradient across the glomerulus and decreases GFR [46].

Treatment of Cardiorenal Syndrome

Loop diuretics remain the cornerstone of treatment of cardiorenal syndrome for effecting natriuresis, net negative salt and water balance, and extracellular volume reduction. Extracellular fluid volume reduction in patients with CHF returns hemodynamics to a more optimal position on the Frank-Starling curve. Reducing volume overload improves renal perfusion pressure by decreasing central venous pressure, renal venous pressure, and right ventricular dilation, which improves right and left ventricular performance. Diuretic resistance remains a challenge and is manifested as a failure to to resolve congestion and a low urine Na despite maximal dose of diuretic. This can occur as a result of inadequate dose, nonadherence, pharmacokinetic factors, CKD, hypotension, hypoalbuminemia, antin-atriuretic drugs, nephron remodeling, and neurohormonal braking. This last phenomenon occurs when diuretics reduce extracellular fluid volume to such an extent that the sympathetic nervous system and angiotensin II production are activated, which then stimulate proximal tubular sodium reabsorption, effectively neutralizing the therapeutic effect of the diuretic [46]. Despite the centrality of diuretics in the management of cardiorenal syndrome, there is a paucity of data to guide their use. The Diuretic Optimization Strategies Evaluation (DOSE) trial was a prospective, double-blind, randomized trial of patients with acute decompensated heart failure that compared intravenous furosemide delivered by either a bolus every 12 hours or by continuous infusion and at either a low dose (equivalent to the patient's previous oral dose) or a high dose (2.5 times the previous oral dose). Co-primary

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endpoints were patients' global assessment of symptoms and the change in serum creatinine level from baseline to 72 hours. At the conclusion, the were no significant differences in patients' global assessment of symptoms or in the change in renal function when diuretic therapy was administered by bolus as compared with continuous infusion or at a high dose as compared with a low dose. However, the high-dose strategy was associated with a greater diuresis [47]. With regard to diuretic dosing regimen, Grodin, et al compared the diuretic effect of a urine output-guided diuretic adjustment and standard therapy for the management of cardiorenal syndrome in acute decompensated heart failure. They showed that compared with a standard diuretic regimen, patients who received stepwise intensification of diuretic therapy had greater net fluid and weight loss without being associated with renal compromise [48]. Another strategy to guide dosing is to follow urine sodium concentrations. An intravenous loop diuretic dose that produces a spot urine sodium <50 mmol/l at 2 hours is inadequate and should generally be doubled until a maximal dose is reached (not clearly defined but often up to a bolus dose of 200 to 300 mg of furosemide equivalents) and urine sodium remeasured. Once an adequate natriuretic response is achieved, the dose can be repeated every 6 to 12 h to achieve the goal net negative sodium balance [49]. Addition of low-dose dopamine or low-dose nesiritide to diuretic therapy in patients hospitalized with acute decompensated heart failure and renal dysfunction were studied in the Renal Optimization Strategies Evaluation (ROSE) trial, which showed that neither had a significant effect on 72-hour cumulative urine volume or change in cystatin C level when compared to placebo [50].

ACE Inhibitors and ARBs

The strength of evidence of ACE inhibitors in HF with predialytic CKD is not established given the lack of inclusion of these patients in RCTs for HF. Both CONSENSUS (Cooperative North Scandinavian Enalapril Survival Study) and SOLVD (Study of Left Ventricular Dysfunction) trial demonstrated the benefits of enalapril for HF symptoms and hospitalization reduction. The enalapril group in SOLVD showed a 33% higher likelihood of a serum creatinine rise of >0.5 mg/dL, but no data on progression of CKD, ESKD, or doubling of creatinine were reported [51] A post hoc analysis of SOLVD with HF and CKD demonstrated a mortality benefit even in subjects with higher degrees of CKD [52]. In a propensity score analysis of 1665 patients with HF (EF <45%) and CKD (eGFR <60 mL/min per 1.73 m^2), treatment with an ACE inhibitor or ARB was associated with significant reductions in all-cause mortality (HR, 0.68 [95% CI, 0.74–0.996]; $P=0.04$) [53]. A recent meta-analysis of data from 3 trials in HFrEF that compared combined neprilysin/RAAS inhibition with RAAS inhibition alone. The trials were the IMPRESS (Inhibition of Metallo Protease by Omapatrilat in a Randomized Exercise and Symptoms Study of Heart Failure; n = 573), OVERTURE (Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events trial; n = 5770), and PARADIGM-HF (Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure; n = 8399). The composite outcome of death or HHF was reduced numerically in patients receiving combined neprilysin/RAAS inhibition in all 3 trials, with a pooled HR of 0.86 (95% CI, 0.76–0.97; $P=0.013$). Combined neprilysin/RAAS inhibition compared with ACE inhibitor alone was associated with more hypotension but less renal dysfunction and hyperkalemia in all 3 trials. [54]. In a subset analysis of PARADIGM-HF, treatment with sacubitril/valsartan resulted a slower rate of decrease in eGFR compared with enalapril, including in patients with CKD, despite a modest increased in albuminuria [55]. The recently published HARP-III trial, investigated the effects of sacubitril/valsartan on kidney function and cardiac biomarkers in patients with moderate to severe chronic kidney disease (GFR 20-60 ml/min/1.73 m^2). Over 12 months, sacubitril/valsartan had similar effects on kidney function and albuminuria when compared with irbesartan, but had the additional effect of lowering blood pressure and cardiac biomarkers. Addition of sacubitril to a patient on RAAS inhibition could further reduce cardiovascular risk in patients with CKD, without further worsening the CKD [56]. Data on the safety and efficacy of Mineralocorticoid receptor antagonists (MRAs in heart failure with advanced CKD are limited. In the EMPHASIS-HF trial (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure), the effect of eplerenone on the primary composite of end point on HHF or cardiovascular death was similar in patients dichotomized at an eGFR <60 mL/min per 1.73 m^2 [57a].

Natriuretic Peptides

B-type natriuretic peptide (BNP) is produced by the myocardial ventricles in response to increased stress. BNP results in arterial and venous vasodilation, increased sodium excretion, and suppression of the renin–angiotensin–aldosterone system.

Nesiritide, a synthetic BNP, was assessed in heart failure patients in the Vasodilation in the Management of Acute Congestive Heart Failure trial [57]. Compared to intravenous nitroglycerine, nesiritide significantly lowered PAOP at 1 hour, although there was no difference in the degree of dyspnea. Nesiritide was equally effective in patients with or without renal dysfunction (Cr > 2.0 mg/dl) [58].

In another trial nesiritide was given to patients with recent increases in baseline Cr associated with congestive heart failure exacerbation (mean Cr increase from 1.5 to 1.8 mg/dl) [59]. Compared to placebo, nesiritide resulted in no changes in urine output, sodium excretion, GFR, or effective renal plasma flow. This finding suggests that nesiritide is ineffective in cardiorenal syndrome.

Additionally, the use of nesiritide in congestive heart failure may be associated with an increased risk of acute

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renal dysfunction and mortality. In a meta-analysis of five randomized trials including 1269 patients, the use of nesiritide was significantly associated with the development of acute renal dysfunction (an increase of Cr of ≥0.5 mg/dl) [60]. Furthermore, in three RCTs that reported mortality rates, the use of nesiritide was associated with a hazard ratio for death of 1.8 ($P = 0.057$) [61].

Ultrafiltration

The CARRESS-HF (Cardiorenal Rescue Study in Acute Decompensated Heart Failure) trial did not show a difference in weight loss with ultrafiltration vs a stepped pharmacologic therapy algorithm in patients hospitalized for acute decompensated heart failure and worsened renal function. However, ultrafiltration was associated with increased creatinine level at 96 hours [62].

A recent Cochrane review looking at the benefits and harms of pharmacological interventions for heart failure in patients with heart failure and CKD concluded that it is uncertain whether these therapies, including nesiritide, make any difference to death, hospitalizations, or adverse effects including worsening kidney function, hyperkalemia, or hypotension [63].

Obstructive Nephropathy

Urinary tract obstruction should always be considered in the differential diagnosis of AKI. Regardless of cause, obstruction of urinary flow leads to renal impairment, which early in the course of the condition is reversible if the obstruction is alleviated. Tubular function is initially affected; however, prolonged obstruction leads to tubular damage and parenchymal atrophy.

Clinical manifestations of urinary tract obstruction vary depending on the location, duration, and degree of obstruction. In patients with complete bilateral obstruction or with an obstructed solitary kidney, anuria (<50 ml urine output in 24 hours) can be the presenting feature, whereas in patients with partial obstruction, the urinary output can vary from oliguria to polyuria. Although pain is more likely to be associated with acute blockage, obstruction may be totally asymptomatic and occur without overt clinical manifestations or suggestive laboratory findings. Therefore, obstructive nephropathy should always be considered as a cause of renal failure when another obvious prerenal failure or intrinsic renal cause is not identified. The location of obstruction is anatomically divided into upper and lower urinary tract at or below the level of the bladder. Common causes of lower urinary tract obstruction include urethral strictures, prostatic hypertrophy, and neurogenic bladder.

Diagnosis of urinary tract obstruction can be difficult. Anuria, flank pain with a palpable mass, or a palpable bladder are obvious clues. Hyperkalemia with a nonanion gap metabolic acidosis is suggestive of a renal tubular acidosis associated with obstruction [64]. The urinary sediment may be bland or demonstrate crystals or hematuria, depending on the etiology of the obstruction. Patients may have very dilute urine due to the presence of an acquired form of nephrogenic diabetes insipidus [65].

Ultrasonography is the most useful test for the presence of obstruction. Although hydronephrosis is usually demonstrated, there are circumstances when hydronephrosis is not seen despite urinary tract obstruction: (i) early in the course of obstruction (12–24 hours) when the collecting system is relatively noncompliant; (ii) in the face of severe volume depletion when glomerular filtration is severely depressed; and (iii) when the collecting system is encased by retroperitoneal lymphadenopathy or fibrosis [66, 67].

Conversely, the finding of hydronephrosis on ultrasound does not prove the presence of obstruction, since it is also seen in high urinary flow states such as diuretic use and diabetes insipidus, pregnancy, previous obstruction, and congenital megaureter. In a series of 192 patients with AKI, hydronephrosis unrelated to obstruction was noted in 11% of patients [68].

Although ultrasound is the preferred imagining modality for initial assessment of obstruction, its use has been supplanted by noncontrast helical computed tomography (CT) scan in the evaluation of flank pain and nephrolithiasis. In a single-center study of 864 patients evaluated for flank pain, 34 underwent both helical CT scan and ultrasound [69]. Compared to helical CT, ultrasound was found to have sensitivity and specificity for renal stones of 81% and 100%, respectively, although the sensitivity for ureteric stones was only 46%. In the same study, the sensitivity and specificity for the detection of hydronephrosis were 93% and 100%, respectively.

In another study, 181 consecutive patients with acute flank pain underwent a combination of helical CT, ultrasound, and unenhanced radiography [70]. When compared with the diagnostic accuracy for ureterolithiasis of combined ultrasound and unenhanced radiography, helical CT had greater sensitivity (92% vs. 77%).

Treatment of obstruction and its timing is dependent on the etiology. Patients with small stones (>5 mm) can be managed conservatively with aggressive hydration and pain control in the absence of infection. Bladder catheterization should be performed if there is reason to suspect that bladder outlet obstruction is present; possible clues to this diagnosis include suprapubic pain, a palpable bladder, or an older man with unexplained renal failure. Measurement of a urinary postvoid residual is often advocated in the detection of outlet obstruction but has not been subjected to any rigorous evaluation. Nor is there a standard method of measurement or definition. Up to one-third of patients with bladder outlet obstruction demonstrated by urodynamic testing do not have an elevated postvoid residual [71]. Upper tract obstruction is relieved with either percutaneous nephrostomy tubes or ureteral stenting, depending on cause, availability, and local expertise.

The duration and severity of obstruction are the major determinants for the recovery of renal function after its correction. The longer the duration of obstruction, the less likely are the chances for complete renal recovery. There are

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few published data on the relationship between duration and obstruction and renal recovery rates. The variability is likely related to the severity and cause of obstruction, the presence of underlying chronic kidney disease, and concurrent infection. Case reports, however, have documented renal recovery after correction of obstruction lasting 12 months [72].

Postobstructive Diuresis

Postobstructive diuresis occurs when there is correction of complete bilateral obstruction or complete obstruction of a solitary kidney. It involves the production of a large volume of urine that results from a defect in urine-concentrating ability, impaired reabsorption of urinary sodium, and solute diuresis from the retained urea and intravenous administration of sodium-containing solutions [73]. Although numerous textbooks discuss the proposed pathogenesis and treatment of postobstructive diuresis, there is very little in the medical literature that describes its clinical course or outcome other than case reports and case series. Patients with relief of complete obstruction are considered at risk for developing postobstructive diuresis. It has been recommended for patients without pulmonary edema, congestive heart failure, or altered consciousness that urine losses be replaced by oral intake. Intravenous fluids are given only if the patients develop orthostatic hypotension, tachycardia, hyponatremia, or a urine output of more than 200 ml/h [74]. In high-risk patients with altered sensorium, congestive heart failure, or pulmonary edema, replacement of half the hourly urine output with half-normal saline has been recommended. If the patient is hyponatremic, normal saline should be used instead. None of these recommendations has been evaluated with rigorous clinical trial. They are considered to be prudent and reasonable based on clinical experience.

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9

Hepatorenal Syndrome

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Renal failure is a common complication in patients with cirrhosis that accounts for major morbidity and mortality [1]. The definition of acute kidney injury (AKI) is based on small changes or a percentage increase serum creatinine from baseline (Table 9.1). A frequent cause of AKI is hepatorenal syndrome (HRS), which is characterized by renal vasoconstriction and a low glomerular filtration rate (GFR) with minimal renal histologic abnormalities. However, establishing the diagnosis of HRS may be difficult because there are no specific diagnostic tests or markers for this syndrome. In addition, patients with liver disease may develop other types of renal impairment such as those related to volume depletion, acute tubular necrosis, drug toxicity and/or glomerular diseases. HRS develops in patients with advanced cirrhosis and ascites; however, it occasionally occurs in patients with alcoholic hepatitis or acute liver failure [1–4]. Although advances in medical therapy of HRS are highly promising, liver transplantation remains the treatment of choice in suitable candidates. Several controlled and uncontrolled studies demonstrate that the use of splanchnic vasoconstrictors, such as terlipressin, midodrine, octreotide, and/or norepinephrine, in combination with albumin as a plasma expander are effective in reducing serum creatinine and increasing GFR to within normal limits. HRS can be effectively prevented in the setting of spontaneous bacterial peritonitis with intravenous albumin [5, 6]. This chapter will review the pathogenesis, clinical features, therapy, and prevention of HRS.

Table 9.1 Definition and staging of AKI.

Definition:
- Increase in serum creatinine ≥0.3 mg/dl (26.5 μmol/l) within 48 h; or
- A percentage increase in serum creatinine of ≥50% which is known, or presumed, to have occurred within the prior 7 days

Staging:
- Stage 1A: An increase in serum creatinine ≥0.3 mg/dl (26.5 μmol/l) or an increase in serum creatinine of ≥1.5-fold to 2-fold from baseline to a value lower than 1.5 mg/dl (133 μmol/l) from baseline to diagnosis of AKI.
- Stage 1B: An increase in serum creatinine ≥0.3 mg/dl (26.5 μmol/l) or an increase in serum creatinine of ≥1.5-fold to 2-fold from baseline to a value ≥1.5 mg/dl (133 μmol/l) from baseline to diagnosis of AKI.
- Stage 2: An increase in serum creatinine greater than twofold to threefold from baseline.
- Stage 3: An increase of serum creatinine greater than threefold from baseline or serum creatinine ≥4.0 mg/dl (353.6 μmol/l) with an acute increase ≥0.3 mg/dl (26.5 μmol/l) or initiation of renal replacement therapy.

Source: Based on Angeli et al. [2].

Pathogenesis

HRS represents the end stage of a circulatory dysfunction that occurs late in the natural history of patients with cirrhosis. The main characteristic of HRS is the presence of renal vasoconstriction, which leads to a functional prerenal AKI. This vasoconstriction is a consequence of a continuous process where several underlying mechanisms interact, including changes in systemic arterial circulation, increased portal pressure, impaired cardiac function, and activation of systemic and renal vasoconstrictor factors (Figure 9.1) [7].

Arterial Vasodilation

Portal hypertension, due to an abnormal liver architecture and increased intrahepatic resistance of blood flow, causes the release of nitric oxide and other vasodilator substances

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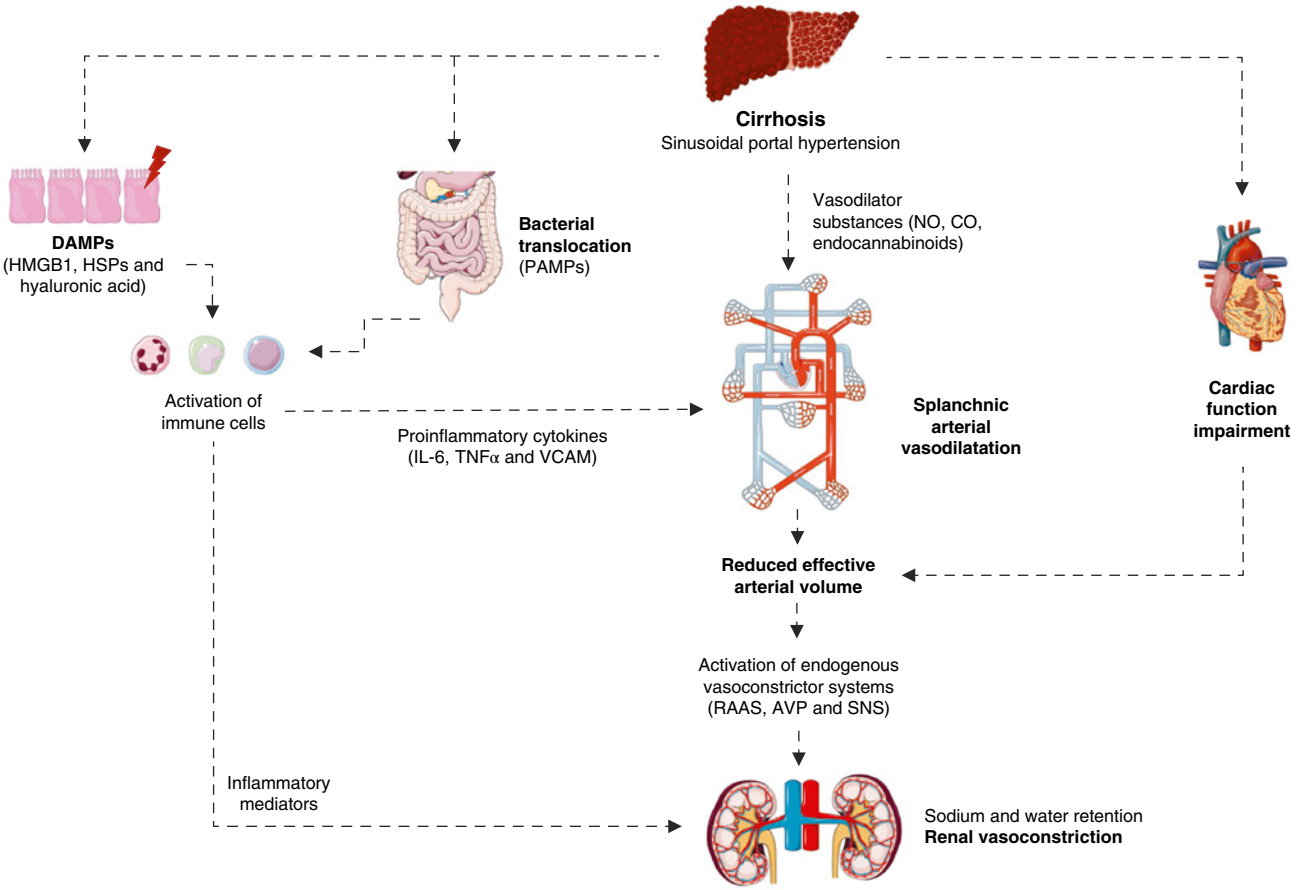

Figure 9.1 Patients with advanced cirrhosis have a marked splanchnic arterial vasodilation triggered by portal hypertension. Splanchnic vasodilation leads to a decreased systemic vascular resistance with the development of effective arterial hypovolemia. The activation of vasoconstrictor systems leads to a marked renal vasoconstriction, low glomerular filtration rate, and development of hepatorenal syndrome. In this advanced stage there is a reduced cardiac output and decreased effective arterial blood volume. Systemic inflammation is altered as well. Pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) of bacterial translocation may lead to a marked inflammatory response. AVP, arginine vasopressin; CO, carbon monoxide; HMGB1, high-mobility group box 1; HSPs, heat shock proteins; NO, nitric oxide; RAAS, renin–angiotensin–aldosterone system; SNS, sympathetic nervous system; TNF, tumor necrosis factor; VCAM, vascular cell adhesion protein.

(i.e. carbon monoxide and endogenous cannabinoids), responsible for splanchnic vasodilatation [8]. Plasma volume accumulates in the splanchnic bed, causing a compensatory response due to a fall in central (effective) blood volume. This activates the renin–angiotensin–aldosterone system (RAAS), the sympathetic nervous system (SNS), and arginine vasopressin (AVP), accounting for sodium and water retention and, in advanced stages, renal vasoconstriction [9–11]. The ongoing action of vasoconstrictor factors acting on the kidney eventually leads to HRS. This occurs because although in the early stages of cirrhosis renal blood flow may be kept within normal limits due to the effect of local renal vasodilators, with time circulating vasoconstrictors overcome the effect of renal vasodilators, leading to severe renal vasoconstriction and reduction in GFR [12, 13]. In some patients precipitating factors such as bacterial infections worsen circulatory dysfunction and may trigger renal vasoconstriction [6, 14]. At this stage, the stimulation of the RAAS, SNS, and AVP is so intense that their vasoconstrictor effects cannot be overcome, and HRS develops.

Reduced Cardiac Output

Circulatory dysfunction in cirrhosis has been the classic defining pathophysiological alteration that leads to HRS; however, evidence suggests that a reduction in cardiac output may play a role as well [15]. As discussed above, a complex interplay between the splanchnic, systemic, and renal circulation comes into play once portal hypertension is established. In the initial stages of cirrhosis in the process of progressive vasodilation, cardiac output (CO) increases to maintain systemic hemodynamic homeostasis. However, with progression to decompensated cirrhosis the

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progressive effects of splanchnic vasodilatation cannot be overcome by increasing CO. Moreover, in patients with ascites or HRS, CO may be normal or even reduced, which is the extreme expression of the circulatory dysfunction [1, 16, 17]. A consequent decrease in effective arterial blood volume may occur, thereby reducing renal perfusion and possibly contributing to the development of HRS. In fact, the development of HRS occurs in the setting of a reduction in CO and the progression of circulatory and renal dysfunction in cirrhosis is not only due to splanchnic vasodilation but also due to a drop in CO. [18–20] In a study of 23 patients with SBP, eight patients who developed renal failure had a significantly reduced cardiac output compared to those that did not develop renal failure [18]. In a second study, 66 patients with cirrhosis and ascites were longitudinally followed. Twenty-seven (41%) developed HRS, and in all cases CO at the time of HRS was significantly decreased compared to the CO in the same patients measured before the occurrence of HRS [19]. The third study, which included 24 patients with decompensated cirrhosis, showed that in patients with a cardiac index (CI) below 1.5 l/min/m^2, GFR and renal blood flow were lower and serum creatinine was higher. Moreover, the number of patients that developed HRS was higher in the group with low CI [20]. These studies support the concept that HRS occurs in the setting of worsening circulatory function, with a significant decrease in CO in the setting of marked splanchnic vasodilation [18–20]. The exact pathogenic mechanisms that cause this decrease in cardiac output are not completely understood.

Systemic Inflammation

Recent evidence indicates that cirrhosis is associated with increased systemic inflammation and that the grade of inflammation is higher with more severe liver, circulatory, and renal dysfunction [21]. Patients with cirrhosis may have elevated white blood cell count, activated circulating neutrophils and monocytes, plasma C-reactive protein (C-RP), pro-inflammatory cytokines, and systemic oxidative stress. The highest levels of inflammatory cytokines in patients with decompensated cirrhosis are seen in those with acute on chronic liver failure (ACLF), in which AKI frequently occurs [22–25].

The main mechanism of systemic inflammation is the translocation of bacteria and/or pathogen-associated molecular patterns (PAMPs) from intestinal lumen to systemic circulation. Bacterial translocation induces an inflammatory response, with increased production of proinflammatory cytokines (particularly interleukin 6 and tumor necrosis factor-α) and vasoactive factors (i.e. NO) in the splanchnic area, leading to a further vasodilation of the splanchnic circulation (Figure 9.1) [26, 27].

Bacterial infections, particularly SBP, are one of the leading triggers of HRS. Patients who develop HRS associated with SBP have higher levels of IL-6 and TNFα compared with those patients with SBP who do not develop HRS [24]. Moreover, a recent study suggested that HRS is characterized by an elevated systemic inflammatory response with higher serum levels of proinflammatory cytokines, particularly IL-6, TNF-α, and VCAM, compared to pre-renal AKI [28].

Renal Vasoconstriction

Marked renal vasoconstriction in individuals with HRS causes reduced perfusion of the renal cortex and this is evidenced by methods such renal arteriography, duplex Doppler ultrasonography, and paraaminohippuric acid excretion among others [29–35]. Renal vasoconstriction is mainly due to the activation of systemic and local vasoconstrictor factors and the suppression of renal vasodilators. Increased angiotensin II as a result of activation of the RAAS causes renal vasoconstriction [19, 36, 37]. Infections such as SBP which can trigger HRS are associated with significant activation of the RAAS. The SNS also plays a role and plasma levels of noradrenaline are greatly increased in patients with HRS compared to those of patients with cirrhosis without HRS. In addition, noradrenaline levels correlate inversely with GFR [38]. Other vasoconstrictor factors such as endothelin and cysteinyl leukotrienes may also play a pathogenic role [39, 40]. A reduced production of endogenous renal vasodilators such prostaglandins has been suggested as playing a pathogenic role in many patients with cirrhosis and ascites. This is supported by the observation that patients with cirrhosis who receive NSAIDs, which inhibit prostaglandin synthesis, can develop AKI resembling HRS [41].

Diagnostic Approach

Patients with cirrhosis may develop AKI for a variety of reasons aside from HRS. Other forms of AKI include those related to hypovolemia and shock, the use of nephrotoxic drugs, and intrinsic renal diseases. AKI occurs in 20–50% of patients with cirrhosis admitted to hospital for complications of the disease. However, HRS appears in about 10–20% of hospitalized patients with cirrhosis and ascites [3]. The probability of developing HRS in patient with cirrhosis and ascites is 18% at 1 year and 39% at 5 years of follow-up [42].

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The initial management of patients with a rising serum creatinine depends on the cause. Therefore, the most important step in treating renal failure in a patient with cirrhosis is to identify its etiology. However, even in the absence of a definitive recognized cause of AKI, the management should be immediately started according to the initial stage (Table 9.1). Irrespective of the stage, diuretics should be discontinued. Similarly, beta-blockers should be temporarily stopped [43]. Other precipitating factors of AKI should be identified and treated, including screening and treatment of infection, volume expansion with albumin when appropriate, Box 9.1 and discontinuation of all nephrotoxic drugs [2]. Volume replacement should be used in accordance with the cause and the severity of fluid loss. Patients with diarrhea or excessive diuresis should be treated with crystalloids, while those with acute gastrointestinal bleeding should be given packed red blood cells to maintain hemoglobin level between 7 and 9 g/dl [44]. In case of no obvious cause, 20% or 25% albumin solution at the dose of 1 g of albumin/kg of body weight (with a maximum of 100 g of albumin) for two consecutive days should be given. An algorithm for diagnosis and management of AKI in cirrhosis is depicted in Figure 9.2.

Clinical Features

Individuals with HRS for the most part exhibit clinical features of advanced cirrhosis, and most have high Model for End-stage Liver Disease (MELD) and Child–Pugh scores, along with low arterial blood pressure and marked urinary sodium retention (urine sodium, ≤10 mEq/l) [42, 46]. The MELD score is a mathematically derived score calculated from serum bilirubin, serum creatinine, and the international normalized ratio for prothrombin time used for organ allocation by liver transplant centers [47]. An updated MELD score including the serum sodium as a variable (MELD-Na) has been implemented in the United States and other countries. This is mainly due to the fact that serum sodium is a strong prognostic factor in patients with advanced liver disease and ascites. In fact, hypervolemic hyponatremia (serum sodium, ≤130 mEq/l) is commonly present in patients with HRS due to increased solute-free water retention because of elevated levels of AVP [48].

AKI and HRS-AKI Criteria

Renal impairment in patients with cirrhosis was previously defined by a serum creatinine value ≥1.5 mg/dl [49]. However, because patients with cirrhosis have a low creatinine production because of reduced muscle mass a low serum creatinine level may result in an overestimation of the GFR [50–52]. A drawback of this cutoff was that it identified patients with a severely reduced GFR (<30 ml per minute) and underestimated the prevalence of this clinical problem. Accordingly, the definition of renal failure in patients with cirrhosis was modified [2]. AKI is now defined as either an absolute increase in serum creatinine of more than or equal to 0.3 mg/dl (≥26.4 lmol/l) in less than 48 hours, or by a percentage increase in serum creatinine of more or equal to 50% (1.5-fold from baseline) in less than 7 days. A new staging system (1A, 1B, 2, and 3) was also introduced, mainly based on the percentage increase of serum creatinine from baseline at the time of the first fulfillment of the criteria together with the value of [53, 54]. This definition has the advantage of detecting earlier phases of kidney dysfunction with the goal of implementing early therapy. Minor increases in serum creatinine detected with the AKI definition are independently associated with increased mortality for hospitalized patients with cirrhosis [55].

Several studies have shown that the new AKI criteria and its stages are prognostic as AKI is associated with increased length of hospital stay and mortality [54, 56, 57]. The definition of the new ICA-AKI criteria also led to changes in the diagnostic criteria of HRS-AKI (Table 9.2). Traditionally HRS was classified into two entities according to severity and progression of kidney failure: type-1 HRS and type-2 HRS [49]. In type 1, patients had a rapid increase of serum creatinine to a level >2.5 mg/dl in <2 weeks and type 2 was characterized with lower serum creatinine levels usually ranging from 1.5 to 2.5 mg/dl. The main change that was made to the classical diagnostic criteria of HRS was the removal of the cutoff value of serum creatinine [2, 45] to allow an earlier diagnosis of HRS-AKI. Therefore, the currently HRS-AKI, includes patients with classical type-1 HRS criteria (serum creatinine ≥2.5 mg/dl), but also those patients presenting with lower values of serum creatinine that fulfill the remaining HRS-AKI criteria and that would not have been included in the classical definition of type-1 HRS. On the other hand, the term type-2 HRS is not included in the current concept of HRS-AKI because is not an acute impairment but rather a chronic impairment of kidney function. Therefore, type-2 HRS is currently considered a form of chronic kidney disease (HRS-CKD) that is characteristic of cirrhosis [2, 45, 58].

Urinary Biomarkers

Differentiating HRS and ATN is quite challenging given that both conditions are common in hospitalized or critically ill patients with cirrhosis. The routine urine biomarkers for

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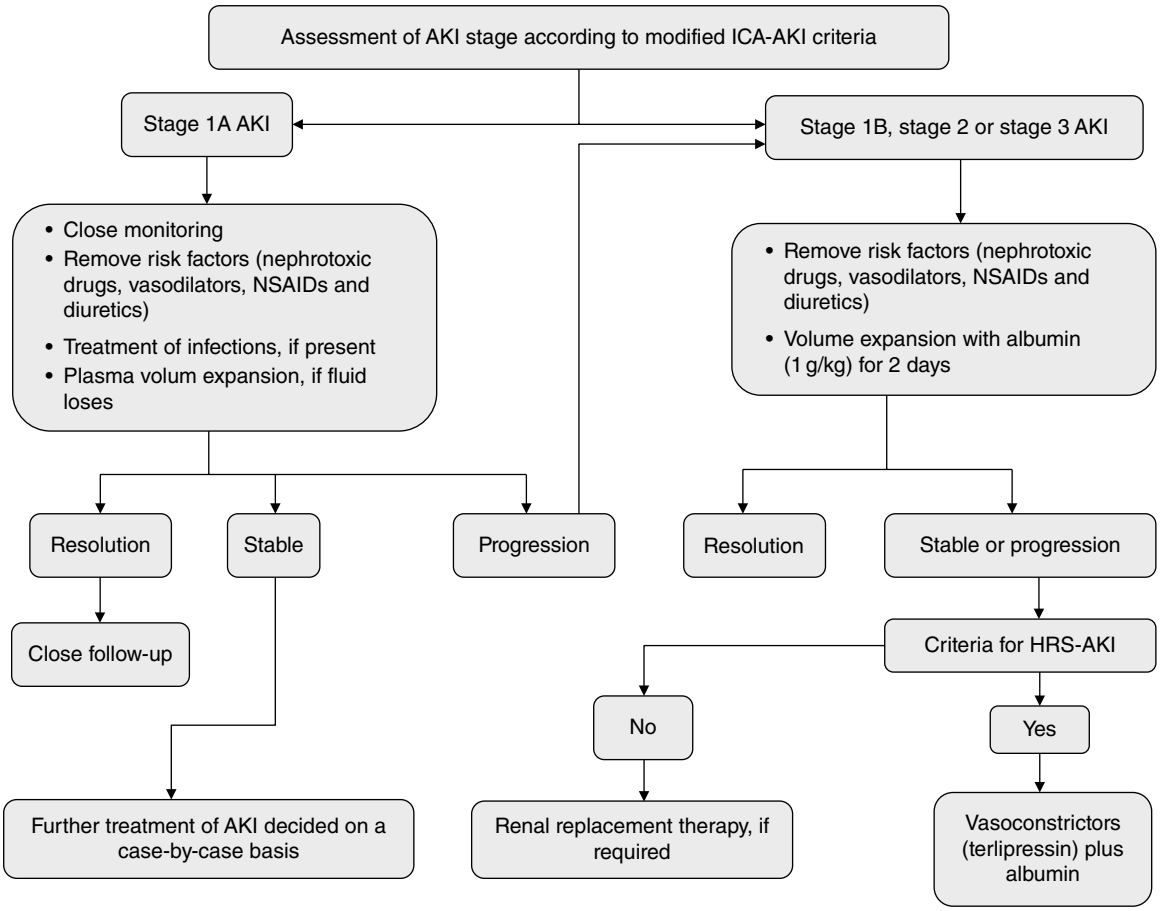

Figure 9.2 An algorithm for diagnosis and management of acute kidney injury (AKI) in cirrhosis. AKI-HRS, AKI-hepatorenal syndrome; ICA-AKI, International Club of Ascites-AKI. [a]Return of serum creatinine levels to <0.3 mg/dl from baseline. [b]Intravenous noradrenaline can be used if terlipressin is not available. The combination of midodrine, octreotide, and albumin is much less effective than terlipressin or noradrenaline plus albumin. *Source:* Modified with permission from Angeli et al. [45].

ATN (urine sodium, fractional excretion of sodium or urine osmolality) are not very useful in patients with cirrhosis because these can be modified by diuretics and also urinary sodium in advanced cirrhosis may be markedly low owing to increased sodium retention [51]. Currently, there are no objective tools with high accuracy for differential diagnosis of AKI, particularly between ATN and HRS-AKI. In this setting, urine biomarkers seem to be very useful in the differential diagnosis and distinguishing structural from functional causes of AKI. The most promising biomarkers are urinary neutrophil gelatinase-associated lipocalin (uNGAL), followed by interleukin-18 (IL-18), albumin, and Liver fatty acid-binding protein (L-FABP) [59–63].

The utility of biomarkers in the field of cirrhosis may be particularly relevant in the differential diagnosis of the type of AKI, especially in distinguishing ATN from prerenal AKI or HRS. The urinary concentration of biomarkers which are upregulated in the setting of tubular injury are increased in patients with ATN compared to patients with prerenal-AKI. uNGAL may help identifying the cause of AKI in patients with cirrhosis, especially in differentiating ATN from HRS [63, 64]. Patients with hypovolemia and

Table 9.2 New diagnostic criteria of acute kidney injury (AKI)-HRS.

- Cirrhosis with ascites
- Diagnosis of AKI according to International Club of Ascites-Acute Kidney Injury (ICA-AKI) criteria
- No response after two consecutive days of diuretic withdrawal and plasma volume expansion with albumin
- Absence of shock
- No current or recent use of nephrotoxic drugs (NSAIDs, aminoglycosides or iodinated contrast media)
- No signs of structural kidney injury. Structural kidney injury is indicated by proteinuria (>500 mg/d), microhaematuria (>50 red blood cells per high-power field), and/or abnormal renal ultrasonography

Source: Based on Angeli et al. [2].

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AKI have low uNGAL levels. The values in patients with HRS are in between those of patients with hypovolemia and AKI and the markedly elevated levels observed among patients with ATN. Moreover, studies suggest that elevated uNGAL is predictive of early mortality in patients with AKI [61]. IL-18 has also been evaluated in patients with cirrhosis, with higher urinary IL-18 levels in patients with ATN as compared to non-ATN AKI [62]. Moreover, urinary IL-18 has also been shown to have a relatively good ability to predict need for renal replacement therapy (RRT) and mortality during hospitalization [61]. Plasma levels of cystatin C seem to be also predictive of AKI in patients with cirrhosis but there are scarce studies. Other urine biomarkers, including albumin and liver fatty acid binding protein have also demonstrated that they have the ability to distinguish ATN from non-ATN in patients with cirrhosis and AKI [59, 62].

Management

The first step of management of patient with HRS is optimization of clinical status with adequate management of fluid balance and blood pressure. Moreover, all patients should have blood, urine, and ascites cultured to rule out bacterial infections. Diuretics should be stopped and low volume therapeutic paracentesis (<5 l) with albumin performed if needed [2, 43, 44] for management of symptoms. Patients need to be hospitalized in a closely monitored acute care unit. A central line may be helpful in assessing volume status after patients receive plasma expansion when ruling out other causes of renal failure, but the routine use of central pressure monitoring has yet to be established. Given that patients are frequently malnourished and require a sodium-restricted diet, a nutritionist should be a part of the team taking care of the patient. Finally, probably the most important aspect of providing care to patients with HRS is assessment of candidacy for liver transplantation. In suitable candidates for liver transplantation, all efforts should be made to improve renal function to obtain a better outcome after transplantation. Current available therapies for HRS-AKI include the use of splanchnic vasoconstrictors and albumin and transjugular intrahepatic portosystemic shunt (TIPS).

Pharmacological Therapy

Although in the past when considering treatment the type of HRS was taken into account, currently it is considered that there is no specific cutoff value of serum creatinine levels for the diagnosis and treatment of HRS-AKI. That said, vasoconstrictor therapy is recommended for those individuals that meet HRS-AKI stage 1B criteria or greater. There is very limited data on the efficacy and side effects of vasoconstrictor therapy in HRS-AKI stage 1a. Systemic vasoconstrictors given with plasma expansion are currently the most effective method form of pharmacologic therapy for HRS [45]. Splanchnic vasoconstrictors are used in conjunction with albumin because they counteract the intense vasodilation of the splanchnic circulation

Box 9.1 Treatment recommendations box, based on GRADE, for AKI-HRS

Comment	Certainty of evidence	Strength of Recommendation
Patients meeting the current definition of **HRS-AKI stage > 1A** should be treated with **vasoconstrictors and albumin**	Moderate	Strong
Terlipressin can be administered by IV boluses (1 mg every 4–6 h) or by continuous IV infusion (2 mg/day)[†]	High	Strong
• In case of **nonresponse** (decrease in SCr <25% from the peak value) after 2 days, the dose of **terlipressin should be increased** in a stepwise fashion to a **maximum of 12 mg/day**		
Albumin solution (20% or 25%) should be used at 20–40 g/day	Moderate	Strong
• Serial assessment of central blood volume aids in titrating the dose		
Noradrenaline can be an alternative to terlipressin[‡]	High	Weak
• Requires a central venous line often in an ICU	Moderate	Weak
Midodrine + octreotide can be an option when terlipressin or noradrenaline are unavailable (but efficacy is lower)		

Source: Modified with permission from EASL CPG decompensated cirrhosis [45].

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and improve effective arterial blood volume, which in turn suppresses the endogenous vasoconstrictor factors responsible for HRS. Vasoconstrictor drugs used in HRS include terlipressin, noradrenaline, and the combination of midodrine and octreotide. Albumin is used concomitantly with these vasoconstrictors as a means of improving effective arterial blood volume and therefore further suppressing endogenous vasoconstrictor factors (RAAS and SNS) responsible for the intense renal vasoconstriction and reduced cardiac contractility in HRS [65–76]. Pharmacological treatment recommentdations are summarized in Box 9.1.

Vasoconstrictors (Table 9.3)

Terlipressin

Terlipressin is the most commonly used drug for HRS in countries in which it is available. It is a synthetic analog of vasopressin and several studies and at least six randomized controlled trials have proven the efficacy of terlipressin plus albumin in the treatment of HRS [65–68, 73, 76, 78]. According to a recent meta-analysis, reversal of HRS occurs in approximately 35–50% of patients with terlipressin plus albumin vs. 11–14% of patients treated with placebo [79]. Also, an improvement in renal function was observed in 48% of patients with terlipressin plus albumin against 24% of patients receiving placebo [79, 80]. Terlipressin plus albumin seems to confer a survival benefit against placebo, but there are some conflicting results [80, 81].

In the initial studies, terlipressin was administered by repeated intravenous boluses (starting dose of 0.5–1 mg every 4–6 hours, increasing to a maximum of 2 mg every 4–6 hours in case of a reduction of baseline serum creatinine <25%) but a randomized trial compared the efficacy and safety of terlipressin given by continuous intravenous infusion (dose 2 mg/d up to 12 mg/d) against intravenous boluses [82]. The study showed similar response rates between both groups. Moreover, mean effective dose of terlipressin was lower in the continuous infusion group, and that was associated with a lower rate of adverse events. The dose of terlipressin should be increased in a stepwise manner if serum creatinine does not decrease by at least 25% with respect to the pretreatment value after 3 days of treatment. Treatment with terlipressin plus albumin should be continued until serum creatinine is <1.5 mg/dl or close to the baseline value before HRS-AKI. In patients with no response or only partial response the treatment should be discontinued within 2 weeks. Recent studies showed that 55.5% of patients with HRS had a complete response to terlipressin plus albumin, defined as a reduction of serum creatinine by >50% to a final value of <1.5 mg/dl [76, 82]. Patients who respond to treatment have a better survival than nonresponders. In two meta-analyses, the use of terlipressin was associated with a significant improvement in short-term survival [80, 83].

Albumin infusion along with terlipressin is always recommended. The combination of albumin and terlipressin is more effective than terlipressin alone [78]. The dose of albumin in HRS treatment has not been well established, but in most studies 20–40 g/d are given. However, the dose of albumin administered is determined by the level of central venous pressure. Aside from an increase in systemic vascular resistance and cardiac output, albumin has nononcotic effects including antioxidative and anti-inflammatory properties [84–87].

Diarrhea and abdominal cramps are common adverse effects of terlipressin (up to 10%). Other more serious adverse events are uncommon (<5%), including ischemic and cardiovascular events. Although rare, patients can develop angina, intestinal, digital or glossal ischemia, cardiac arrhythmias, or severe hypertension. Patients with established ischemic heart disease and peripheral vascular disease should not be treated with terlipressin.

Norepinephrine, Midodrine, and Octreotide

The use of vasoconstrictors other than terlipressin is an alternative in countries where terlipressin is not available. Noradrenaline is an (alfa)-adrenergic and (beta)-adrenergic receptor agonist with vasoconstrictor effect activity on splanchnic circulation that can also improve renal perfusion. It has been evaluated in four randomized controlled trials compared to terlipressin [69–72]. A meta-analysis compared terlipressin plus albumin with noradrenaline plus albumin and found no difference in the reversal of HRS, 30-day mortality and recurrence of HRS [80]. Although data is limited due to the low number of patients included in the studies ($n = 78$), noradrenaline seems to be as effective as terlipressin in the management of HRS and represents a good alternative treatment [80], however the quality of evidence supporting the use of noradrenaline is low according to a meta-analysis [80]. Noradrenaline must be administered under continuous monitoring and in some countries it cannot be used outside intensive care units.

Midodrine, a selective (alfa)-1-adrenergic receptor agonist, and octreotide, a somatostatin analog, have been evaluated in the management of HRS; there are no placebo-controlled trials and only nonrandomized observational cohort studies in very small series of patients demonstrate a mild improvement in renal function and GFR with suppression of renin, aldosterone, norepinephrine, and vasopressin to normal or near-normal levels [88, 89]. However, this data was not confirmed in a recent randomized control trial, where midodrine and octreotide plus albumin were compared to terlipressin plus albumin, and significant higher response rates were

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Table 9.3 Studies evaluating vasoconstrictors in patients with HRS.

Study (reference)	Study design	Reversal HRS (%)[a]	Recurrence[b]	Reversal HRS in control group	Treatment related severe side effects[c] (%)	Median survival (days)	Median survival, control group (days)
Terlipressin vs. placebo or control							
Prashant et al. [65]	Single-center, single blind, placebo-controlled, randomized trial	5/12	NA	0/12	3/12	NA	NA
Neri et al. [66]	Single-center, open-label, randomized controlled trial	21/26	NA	5/26	2/52	87% at day 15, 72% at day 30, 67% at day 60, 54% at day 90, 42% at day 180	53% at day 15, 42% at day 30, 21% at day 60, 18% at day 90, 16% at day 180
Sanyal et al. [67]	Multicenter, double-blind, placebo-controlled trial	19/56	1/9	7/56	5/56	24/56 at day 180	21/56 at day 180
Martín-Llahí et al. [73]	Multicenter, open-label, randomized controlled trial	9/23	1/10[d]	1/23	10/23	6/23 at day 90	4/23 at day 90
Zafar et al. [77]	Single-center, randomized controlled trial	10/25	NA	2/25	NA	NA	NA
Boyer et al. [68]	Multicenter, double-blind, placebo-controlled, randomized trial	19/97	3/19	13/99	14/93[e]	23.8 56/97 at day 90	20.7 days 54/99 at day 90
Noradrenaline vs. terlipressin							
Alessandria et al. [72]	Single-center, open-label, randomized controlled trial	7/10	2/7	10/12	0/10	NA	NA
Indrabi et al. [69]	Single-centre, randomized controlled trial	16/30	1/16	17/30	NA	37.7 ± 49.9	45.6 ± 44.1
Sharma et al. [70]	Single-center, open-label, randomized controlled trial	10/20	NA	10/20	5/40	15	13
Singh et al. [71]	Single-center, open-label, randomized controlled trial	9/23	0/9	10/23	0/46	9/23 at day 15, 7/23 at day 30	11/23 at day 15, 8/23 at day 30
Midodrine plus octreotide vs. terlipressin							
Cavallin et al. [76]	Multicenter, open-label, randomized controlled trial	1/21		15/27	13/48	14/21 at day 30, 9/21 at day 90	19/27 at day 30, 16/27 at day 90
Midodrine plus octreotide vs. noradrenaline							
Tavakkoli et al. [75]	Single-center, open-label, randomized controlled trial	9/12	3/9	8/11	0/23	NA	NA

[a] The definition of response varied between studies, but in all studies it was defined as a marked decrease in serum creatinine.
[b] Recurrence of HRS after treatment withdrawal in responder patients; the definition of recurrence also varied between studies.
[c] Many patients presented with self-limited abdominal cramps and/or diarrhea during the administration of the first doses of terlipressin, which were not counted as severe side effects.
[d] 10 out of 23 improve renal function, nine with complete response.
[e] Eight patients (four in each treatment group) did not receive study medication primarily because of declining health and SCr levels that did not meet inclusion criteria after randomization.

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found in the terlipressin group (70.4% vs. 28.6%) [76]. Therefore, terlipressin is clearly more effective than the combination of midodrine and octreotide.

Aim of Pharmacological Therapy

The most important objective when treating HRS-AKI is to reverse renal failure to provide a successful bridge to liver transplant so that suitable candidates can undergo transplantation with less morbidity and side effects to post-transplant medications and have similar outcomes as patients without HRS-AKI. As mentioned above, response to therapy is considered when there is marked reduction of the high serum creatinine levels, at least below 1.5 mg/dl, which is usually associated with increased urine output and improvement of hyponatremia [45]. Studies suggest that response to treatment with vasoconstrictors and albumin correlates with an increase in mean arterial pressure (MAP). One study showed that patients who experienced a significant increase in MAP during terlipressin treatment had a higher probability of recovering kidney function [90]. Another study also reported that responders to terlipressin had a higher increase in MAP at the end of treatment compared with nonresponders. The improvement of kidney function in patients with HRS treated with vasoconstrictors tightly correlates with the rise in MAP. Therefore, a goal-directed approach to the treatment of HRS based on targeting a rise in MAP during vasoconstrictor therapy may lead to better outcomes [90–92]. Nevertheless, prospective studies evaluating this approach are needed before integrating it into practice. Recurrence of HRS in responders, after the end of the treatment, has been reported in up to 20% of cases. Re-treatment is usually effective, but in some cases continuous recurrence occurs. Patients who respond to treatment with terlipressin plus albumin show a better survival than nonresponders to treatment.

Nonpharmacological Therapy

Liver Transplantation

Liver transplantation is the best available effective therapy for patients with HRS-AKI since it cures liver failure and portal hypertension. Since patients with HRS-AKI have a poor prognosis, this group of patients should be given higher priority for transplantation [93]. In fact, the implementation of the MELD score in many countries has placed these patients at a higher priority level for liver transplant because serum creatinine is a strong variable in the mathematical model [47]. The presence of HRS-AKI at the time of liver transplantation has a negative impact on survival after the operation. Patients with HRS who undergo transplantation have more complications, spend more days in the intensive care unit, and have a higher in-hospital mortality rate than transplanted patients without prior HRS [94].

Although liver transplantation is the treatment of choice, renal function does not completely recover in all patients [94, 95]. The reason for this is not known. Simultaneous liver-kidney (SLK) has been considered for patients with HRS. Recent recommendations for SLK in the United States include patients with AKI with an estimated GFR of $\leq 25\,ml/min/1.73\,m^2$ for 6 weeks or a period of dialysis ≥ 6 weeks, patients with an eGFR of $< 45\,ml/min/1.73\,m^2$ for > 90 days (stage 3B, 4, or 5 CKD), or patients with comorbidities and presence of metabolic diseases [96]. European guidelines suggest that patients with end-stage liver disease who have a GFR of $< 30\,ml/min/1.73\,m^2$ or type 1 HRS requiring RRT of > 8–12 weeks and patients with renal biopsy samples revealing $> 30\%$ fibrosis and glomerulosclerosis should receive simultaneous liver and kidney transplant [45]. SLK is also indicated in patients with cirrhosis and sustained AKI irrespective of its type, including HRS-AKI when refractory to drug therapy if requiring RRT for ≥ 4 weeks, or if the estimated GFR is $\leq 35\,ml/min/1.73\,m^2$ or measured GFR $\leq 25\,ml/min/1.73\,m^2$ for ≥ 4 weeks [45]. Beyond these two conditions, in a candidate with high priority for liver transplantation due to a high MELD score, the option of SLK may be considered in the presence of risk factors for underlying undiagnosed CKD (diabetes, hypertension, abnormal renal imaging, and proteinuria $> 2\,g/d$) [45].

Transjugular Intrahepatic Portosystemic Shunt

Transjugular intrahepatic portosystemic shunt (TIPS) is a nonsurgical intervention performed percutaneously that creates a connection (by means of a prosthetic shunt) within the liver between the portal and hepatic vein, thereby reducing portal pressure. This method has been used as an alternative therapy to surgical shunts for cirrhotic patients bleeding from esophageal or gastric varices who are refractory to endoscopic and medical treatment. The rationale for using TIPS in HRS is based on the fact that reduction of portal pressure improves circulatory function and suppresses RAAS and SNS activity. Four uncontrolled studies indicate that TIPS may improve renal function and GFR as well as reduce the activity of RAAS and SNS in patients with cirrhosis and HRS. Improvement in renal function observed in these uncontrolled

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studies after TIPS placement alone was slow and successful in approximately 60–70% of patients. However, studies assessing TIPS for type 1 HRS have only included patients with preserved liver function and excluded those with a history of hepatic encephalopathy, Child–Pugh scores of ≥12, or serum bilirubin of >5 mg/dl. As existing data are limited and the applicability of TIPS in these patients is very low, TIPS placement should not be recommended in the setting of HRS-AKI [89, 97, 98].

Renal Replacement Therapy

RRT is not recommended as a first-line treatment in patients with HRS-AKI, but it should be considered in nonresponders to vasoconstrictors. Indications for RRT are the same in patients with cirrhosis as in the general population, including severe and/or refractory electrolyte or acid-base imbalance, severe or refractory volume overload, and/or symptomatic azotemia. However, published data on RRT in patients with cirrhosis are scant, with controversial effects on survival [99, 100]. Alternative dialysis methods such as the molecular adsorbent recirculating system (MARS) and albumin dialysis have been evaluated. These systems remove protein-bound solutes from plasma, such as bilirubin, bile acids, and cytokines, that are not well removed by conventional hemodialysis or hemofiltration. Although these treatments may have some potential beneficial effect, they should still be considered experimental and further controlled studies are clearly needed before advocating their use in the management of patients with HRS [101, 102]. Treatment guidelines do not recommend MARS for the management of HRS in clinical practice.

Prevention

In SBP, intravenous albumin (1.5 g/kg at diagnosis of infection and 1 g/kg 48 hours later) mitigates the risk of development of HRS because it counteracts an enhanced arterial splanchnic vasodilation triggered by the infection, causing an even more reduced effective arterial blood volume with additional activation of vasoconstrictor systems. The incidence of HRS in patients with SBP not administered albumin was 33% and only 10% in those who received albumin. In addition, there was less in-hospital mortality in those receiving albumin (10%) than in those not receiving albumin (29%) [6]. Albumin is not effective in the prevention of HRS associated with infections other than SBP [103, 104]. Prophylaxis with norfloxacin in patients with cirrhosis and ascites reduces the incidence of SBP and delays the development of HRS, but can increase the risk of infections caused by multidrug-resistant organisms [105]. Previous studies suggested that the use of pentoxyfilline decreased the incidence of renal failure in patients with alcoholic hepatitis. However, recent data do not confirm these results [106–109].

Summary

HRS-AKI is a devastating complication of patients with cirrhosis and ascites. Triggers of AKI such the use diuretics and nephrotoxic drugs, infections, hypovolemia, and parenchymal kidney disease should be sought for and promptly managed. Differential diagnosis of HRS-AKI from other forms of AKI, such as ATN, is often difficult. Specific biomarkers such as NGAL or IL-18 may aid in the correct diagnosis of AKI in cirrhosis but have not yet been introduced into clinical routine. Vasoconstrictors such as

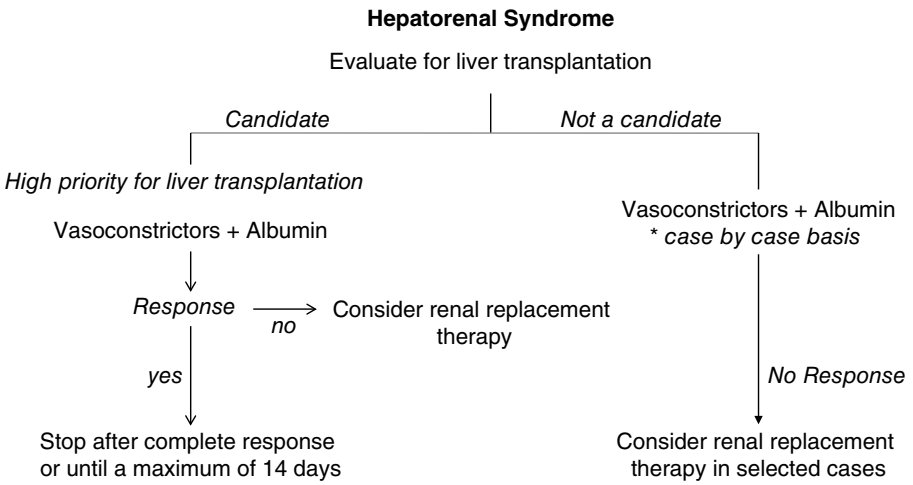

Figure 9.3 Treatment algorithm of AKI-HRS depending on whether the patient can undergo liver transplantation.

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terlipressin and noradrenaline in combination with intravenous albumin are the first-line therapy for HRS-AKI. Liver transplantation is considered a definitive and effective treatment for HRS and patients with cirrhosis and HRS-AKI should be prioritized for liver transplantation. An algorithm for management of AKI in cirrhosis is summarized in Figure 9.3.

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10

Acute Tubular Necrosis

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Introduction

Acute kidney injury (AKI) is defined as a rapid deterioration in kidney function resulting in a reduction in glomerular filtration rate (GFR) and a failure of the kidneys to excrete nitrogenous waste products and to maintain fluid, electrolyte, and acid-base balance [1]. The two most common etiologies of AKI are prerenal azotemia, caused by reversible renal hypoperfusion, and acute tubular necrosis (ATN) [2–6]. ATN results from intrinsic parenchymal damage mediated by endothelial and epithelial cell injury, intratubular obstruction, and immunologic and inflammatory processes. ATN is a histopathologic and pathophysiologic entity that can stem from a variety of distinct renal insults, often seen in combination, and these can be divided broadly into ischemic (prolonged volume depletion, hypotension), septic, and nephrotoxic (medications, radiocontrast dye, rhabdomyolysis) categories [2]. Ischemic ATN is seen most commonly and occurs on a continuum beginning with prerenal azotemia [1, 5]. When prerenal insults are severe or prolonged they may give rise to tubular damage [1]. Histology reveals dilation of proximal tubular lumens, flattening of the tubular epithelium, simplification and loss of brush border, and vacuolization (Figure 10.1) [7]. These histological changes are reflected in the urinalysis, which typically reveals the presence of cellular debris and "muddy brown casts" which consist of sloughed and necrotic epithelial cells (Figure 10.2) [8].

ATN is common, however the incidence and outcomes vary significantly depending on the definition used and the patient population studied [2]. The landmark Program to Improve Care in Acute Renal Disease (PICARD) study was an observational study of a cohort of 618 patients with AKI in the intensive care units (ICUs) of five academic centers in the United States. Ischemic ATN was the presumed etiology for 50% of all patients with renal failure, while an additional ~12% were attributed to unresolved prerenal factors and ~25% to nephrotoxic ATN [5]. It is important to note that the diagnosis of ATN is often inferred based upon clinical characteristics, since kidney biopsies are not routinely performed in patients with AKI. While several classes of agents have been investigated, thus far no specific pharmacologic strategies have proven effective for preventing or treating ATN. Therefore, it is essential that clinicians focus on preventative measures such as maintaining adequate systemic perfusion and limiting nephrotoxin exposure, especially in those deemed to be at highest risk.

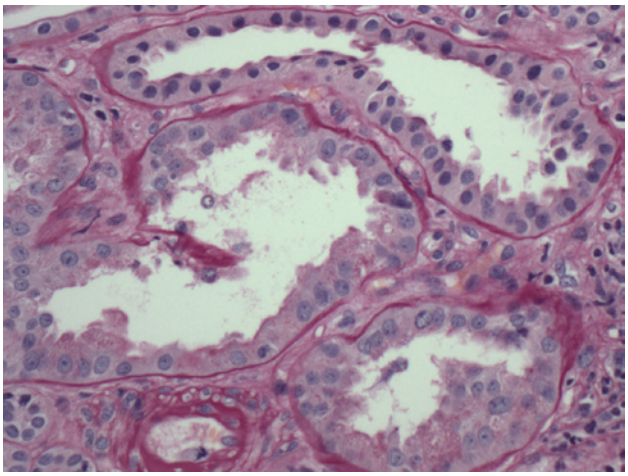

Figure 10.1 High-power image demonstrating flattened epithelium with loss of the brush border and cells becoming disconnected from the basement membrane as seen in acute tubular necrosis. *Source:* Image courtesy of Helen P. Cathro, University of Virginia Health System, Division of Renal Pathology.

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Figure 10.2 Muddy brown casts as seen in a patient with acute kidney injury and presumed acute tubular necrosis due to sepsis.

Definition

ATN is a histopathologic and pathophysiologic entity that is the end result of numerous ischemic, nephrotoxic, and inflammatory insults. In many cases, the decline in kidney function may be more prominent than the severity of histologic change, and necrotic cell death may not be readily apparent [2, 9–11]. Clinical manifestations of ATN vary by patient and the type of insult. While some patients maintain normal urine flow, others may develop a decline in urine output (oliguria) and subsequent signs and symptoms of volume overload. Similar to the metabolic derangements seen in other forms of AKI, reduced GFR and impaired tubular function in ATN may lead to hyperkalemia, metabolic acidosis, and azotemia. These may range from mild to severe and life-threatening. In some cases, other kidney manifestations of a toxic insult may be present such as glomerular disease (nonsteroidal anti-inflammatory agents) or tubular dysfunction such as the Fanconi syndrome (ifosfamide) or sodium and magnesium wasting (cisplatin).

Epidemiology

While it is clear that AKI is commonly encountered in clinical practice, the reported incidence varies depending on the definition used and the patient population evaluated [2, 12, 13]. In one study of 20 126 patients with a mean age of 64 years admitted to an Australian tertiary care hospital, almost 20% of patients met criteria for AKI as defined by the RIFLE (Risk, Injury, Failure, Loss, and End-stage) criteria. Importantly, multivariate logistic regression analysis showed that all RIFLE criteria were significantly predictive factors for hospital mortality, with an almost linear increase in odds ratios (ORs) from Risk to Failure (ORs: Risk 2.5, Injury 5.4, Failure 10.1) [13]. An even higher incidence of AKI has been demonstrated in the intensive care setting, with one retrospective cohort study of 5383 patients admitted to the ICUs of a single tertiary care academic center revealing an AKI incidence of 67%. Again, increased hospital mortality was seen with progressive RIFLE stage [12].

The vast majority (two thirds or more) of cases of AKI in hospitalized patients can be attributed to ATN or prerenal injury [3–6]. This attribution is often based upon compatible history and diagnostic findings and not based upon histology, and to our knowledge there are no studies that have systematically evaluated the causes of AKI in hospitalized patients based on biopsy findings. In a study by the Madrid Acute Renal Failure Study Group, ATN was identified in 45% of patients, while prerenal azotemia was determined to be the cause of AKI in 21% of patients [4]. In the PICARD study, an observational cohort study of 618 patients with AKI in the intensive care setting, ischemic ATN occurred in >50% of cases, while nephrotoxic ATN played a role in 25% of cases [5].

Certain patients and populations are at greater risk for the development of ATN based on age, comorbidities, severity of illness, and exposures to procedures and medications. The elderly, diabetic patients, those with preexisting chronic kidney disease (CKD) or hypertension, those with renal artery stenosis, and those taking nonsteroidal anti-inflammatory drugs (NSAIDs), angiotensin-converting-enzyme (ACE) inhibitors, or angiotensin-receptor blockers (ARBs) may be at increased risk for ischemic ATN due to impaired renal autoregulation [9]. The combination of an ACE inhibitor or an ARB along with an NSAID is a particularly high-risk scenario especially in states of volume depletion, where renal autoregulation and perfusion can be severely impaired [14]. Other populations at high risk for the development of ATN include (i) patients in ICUs, where 35–56% of cases of AKI are attributed to sepsis; (ii) postoperative patients, in particular those underdoing abdominal aortic aneurysm surgery, surgery to correct obstructive jaundice, or combined coronary artery bypass graft (CABG) surgery with valve surgery; and (iii) patients receiving iodinated radiocontrast dye (especially when delivered intra-arterially and at high doses) [2, 15–22].

Pathophysiology

Histology

The histologic lesions of ATN predominantly affect the proximal tubules (PTs) and vary with the severity of kidney injury and the stage of evolution of the lesion. On light

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microscopy, ATN typically manifests as dilation of proximal tubular lumens, flattening of the tubular epithelium, simplification and loss of brush border, and vacuolization (see Figure 10.1) [7]. Downstream, distal tubular casts and obstruction may be present and result from the binding of desquamated tubular cells and debris to Tamm-Horsfall protein [23]. Interstitial edema with mild to moderate leukocyte infiltration can be seen. Morphologic changes may be subtle, and frankly necrotic cells may not be present even in those with marked functional impairment [2, 9–11]. For this reason, many clinicians and pathologists prefer the term "acute tubular injury" (ATI) to "ATN" [11].

Ischemic ATN

Phases of Ischemic ATN

Much remains to be discovered about the complex biology of ATN. Current research suggests that the course of ischemic ATN progresses across five phases: prerenal, initiation, extension, maintenance, and repair. During the *prerenal* phase, alterations in renal blood flow (RBF) lead to a decrease in intraglomerular pressure, however a variety of cellular and vascular adaptations are able to maintain renal epithelial integrity [24]. These alterations may be the result of volume depletion (vomiting, diarrhea, use of diuretics), hypotension (shock), cirrhosis (splanchnic vasodilation), heart failure (primarily through venous congestion and increased intra-abdominal pressure), selective renal ischemia (renal artery stenosis, cross-clamping of the renal artery during surgery for renal cell carcinoma), or drugs that cause afferent arteriolar constriction (NSAIDs, calcineurin inhibitors) or efferent arteriolar dilation (ACE inhibitors, ARBs) [1, 25]. The *initiation* phase of ischemic ATN occurs when hypoperfusion is sufficiently severe or prolonged to deplete adenosine triphosphate (ATP), leading to tubular cell injury and a continued decline in GFR [24]. The subsequent *extension* phase is characterized by (i) vascular endothelial damage, which contributes to severely reduced blood flow, persistent hypoxia, microvascular obstruction, coagulopathy, and further injury to tubular epithelial cells; and (ii) a pronounced inflammatory response mediated by an influx of leukocytes and the release of chemokines and cytokines that enhance the inflammatory cascade [24]. During the *maintenance* phase, GFR nadirs as cells undergo migration, apoptosis, and proliferation in an attempt to reestablish cellular and tubular integrity. Blood flow returns toward normal. Finally, during the *recovery* phase, GFR begins to improve as cellular differentiation and repair occur. It is in this phase that epithelial polarity is reestablished and cellular and organ function is restored [1, 24]. Incomplete recovery and/or conversion from a physiological to a pathological repair response, driven by a combination of improper tubule repair, vascular dropout, hypoxia, and persistent activation of the immune system may lead to fibrosis and CKD [24].

Tubular Factors

The abrupt fall in GFR seen in ATN has traditionally been attributed to an interplay between tubular and hemodynamic abnormalities [26]. Ischemic insults to the kidney preferentially cause cell damage and death of tubular epithelial cells, leading to decreased kidney function. These cells are especially susceptible to ischemic injury because of their high demand for oxygen and ATP to drive transport functions, along with their location in an environment of very low oxygen tension [27]. Cells in the S3 segment of the PT and the thick ascending limb of Henle are most prone to ischemic injury due to a combination of low medullary blood flow and countercurrent diffusion of oxygen causing lower partial pressure of oxygen (pO2) [28].

Renal ischemia leads to a loss of cytoskeletal integrity and cell polarity, with shedding of both necrotic and viable PT brush border cells into the tubule lumens [2]. This is thought to be driven, in part, by redistribution of sodium/potassium ATPase and integrins from the basolateral to the apical membrane [29–31]. Additional biochemical pathways that have been implicated in severe cell injury and ATN include (i) depletion of ATP; (ii) increased tissue concentrations of reactive oxygen species; (iii) intracellular acidosis; (iv) increased concentrations of cytosolic calcium; (v) increased activity of phospholipases; (vi) release of proteases from the tubular cell brush border; (vii) mitochondrial injury; and (viii) cell apoptosis [2, 26, 32, 33]. As cells desquamate and enter the lumen, backleak of filtrate may occur into the vascular space across the damaged tubular epithelium, potentially contributing to further decline in GFR, especially when intratubular pressure is increased due to intratubular obstruction [26, 34].

Renal Blood Supply

In ATN, RBF can decrease by as much as 30–50%, with a disproportionate decrease in medullary blood flow relative to total RBF contributing to pronounced medullary ischemia [2, 35–38]. A variety of mechanisms have been proposed to explain this and include (i) increased vasoconstriction in response to endothelin, adenosine, angiotensin II, thromboxane A_2, leukotrienes, and sympathetic nerve activity; (ii) decreased vasodilation in response to nitric oxide, prostaglandin E_2, acetylcholine, and bradykinin; (iii) structural damage to endothelial and vascular smooth muscle cells; and (iv) increased leukocyte-endothelial adhesion, vascular obstruction, leukocyte activation, and inflammation from release of chemokines and cytokines [32]. In addition, the combination of continued

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filtration and impaired tubular reabsorptive function leads to increased sodium chloride delivery to the macular densa, ultimately activating tubuloglomerular feedback (TGF) and causing afferent arteriolar constriction with resultant further decline in GFR [32, 39].

Septic ATN

Sepsis is a frequent cause of AKI in hospitalized patients [15, 16, 20, 21]. While previously thought to induce ATN through decreased renal perfusion and systemic hypotension, more recent data suggest that septic ATN may be associated with systemic vasodilation, high-output cardiac failure, and increased RBF ("hyperdynamic sepsis"). In one study of ewes treated with *Escherichia coli* infusion to induce sepsis, RBF was found to be significantly increased. Importantly, recovery from sepsis was associated with relative renal vasoconstriction and return in RBF back to control levels [40]. In a follow-up study, sepsis induced by *E. coli* was again associated with increased RBF, along with oliguria and reduced GFR. Infusion of angiotensin II restored arterial pressure, decreased RBF, and led to a significant increase in urine output and normalization of creatinine [41]. One possible explanation for these findings is that kidney injury in this state may occur due to preferential dilation of the efferent arteriole, leading to a decrease in intraglomerular pressure and drop in GFR [42].

Nephrotoxic ATN

Nephrotoxic ATN may be associated with exposure to a variety of exogenous and endogenous toxins, some of which are shown in Table 10.1. Exogenous toxins include medications that impair renal autoregulation and predispose patients to prolonged prerenal ischemia and subsequent ATN (NSAIDs, ACE inhibitors, ARBs), as well as drugs that are directly toxic to renal tubules, including many antimicrobial, iodinated radiocontrast, and antineoplastic agents. Other exogenous toxins, such as acyclovir and methotrexate, may cause ATN through intratubular crystal precipitation and obstruction. ATN secondary to the production of endogenous toxins may occur in patients with rhabdomyolysis or, less commonly, hemolysis. In these cases, AKI is caused by the release of heme pigment from myoglobin and hemoglobin, respectively, ultimately leading to (i) tubular obstruction; (ii) direct proximal tubular cell injury; and (iii) vasoconstriction with reduced medullary blood flow [43, 44]. Additionally, endogenous production of abnormal paraproteins (as in multiple myeloma) and uric acid (as in tumor lysis syndrome) may injure renal tubules through precipitation and intratubular obstruction [45].

Table 10.1 Mechanisms of nephrotoxin-induced acute tubular necrosis.

Mechanism of injury	Toxin
Exogenous toxins	
Altered intraglomerular hemodynamics (prolonged prerenal injury predisposing to ATN)	Afferent vasoconstriction: NSAIDs Calcineurin inhibitors Iodinated radiocontrast agents
	Efferent vasodilation: ACE inhibitors ARBs
Direct tubular toxicity	Antimicrobials: Aminoglycosides, outdated tetracyclines, vancomycin Amphotericin B Cidofovir, tenofovir Pentamidine
	Antineoplastic agents: Cisplatin Ifosfamide
	Recreational drugs: Synthetic cannabinoids
	Miscellaneous: Acetaminophen Calcineurin inhibitors Iodinated radiocontrast agents Mannitol Sucrose-containing IVIG formulations Zoledronate
Intratubular obstruction	Acyclovir, indinavir, methotrexate, sulfonamides
Endogenous toxins	
Intratubular pigments	Rhabdomyolysis (may be precipitated by medications [statins, haloperidol] and drugs of abuse [cocaine, alcohol])
	Hemolysis (may be precipitated by quinine, quinidine, sulfonamides)
Intratubular obstruction by proteins	Multiple myeloma (cast nephropathy)
Intratubular precipitation	Uric acid (tumor lysis syndrome)

ACE, angiotensin-converting-enzyme; ARB, angiotensin-receptor blocker; ATN, acute tubular necrosis; IVIG, intravenous immunoglobulin; NSAID, nonsteroidal anti-inflammatory drug.
Source: Adapted by permission from Rosner MH, Okusa MD (2008). Drug-associated acute kidney injury in the intensive care unit. Clinical Nephrotoxins, 29–41. © 2008, Springer Nature.

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Diagnosis

History and Physical Examination

Determining the etiology of AKI begins with a careful evaluation of the patient's history and physical examination. For example, a history of vomiting, diarrhea, or hypotension, combined with physical examination findings of volume depletion, may point toward prerenal AKI or ischemic ATN. Recent exposure to nephrotoxic medications or iodinated radiocontrast dye may suggest nephrotoxic ATN. A careful and thorough history of drug and other potential nephrotoxin exposure is critical.

Urine Sodium Concentration and Fractional Excretion of Sodium

Fractional excretion of sodium (FENa) is a measure of the extraction of sodium and water from the glomerular filtrate; it is the ratio of the sodium filtration rate to the overall GFR as estimated by the renal filtration of creatinine:

$$\frac{[\text{urine sodium}]\times[\text{plasma creatinine}]\times 100}{[\text{plasma sodium}]\times[\text{urine creatinine}][46]}$$

FENa has traditionally been used to distinguish between prerenal azotemia and intrinsic forms of AKI such as ATN in patients with oliguria. In cases of prerenal AKI, and in early ischemic ATN where tubular function remains intact, urinary sodium concentration (UNa) should be low (<20 mmol/l) and FENa should be <1%, while in established ATN with impaired tubular function, UNa will be higher (usually >40 mmol/l) and FENa will be >1% [2, 46].

While these urine indices may help differentiate prerenal azotemia from ATN in some cases, there are limitations to the use of UNa and FENa. For example, in the presence of CKD or diuretic use, the diagnostic accuracy of urine chemistries to distinguish these conditions decreases. A low fractional excretion of urea (FEUrea) (<35%) is more sensitive than FENa for distinguishing prerenal from intrinsic renal failure when diuretics have been recently administered [47]. For instance, in a prospective study of AKI patients, a FEUrea ≤35% was less sensitive than a FENa ≤1% in differentiating between prerenal disease and ATN in patients not treated with diuretics (48% vs. 78%) and was more sensitive (79% vs. 58%) but less specific (33% vs. 81%) in patients who were treated with diuretics [47]. Additionally, ATN in the setting of rhabdomyolysis, hemolysis, sepsis, or recent contrast administration has been shown to be associated with low UNa (<10 mmol/l) and FENa <1% [48–52]. Given these limitations, measurements of UNa and FENa must be interpreted in the context of patient's overall clinical course and exposure history.

Urine Microscopy

The histologic changes of ATN are reflected in the urinalysis, which classically reveals the presence of cellular debris and "muddy brown casts" consisting of sloughed and necrotic epithelial cells. Perazella and colleagues demonstrated the high value of urine microscopy for the diagnosis of ATN using a urinary sediment score. In patients with a high pretest probability of ATN, the presence of any casts or renal tubular epithelial (RTE) cells (score ≥2) resulted in very high positive predictive value (100%) and low negative predictive value (44%) for a final diagnosis of ATN [8]. In a subsequent study, the same group determined that a urinary sediment score may be useful to predict worsening of kidney injury due to ATN during hospitalization [53]. A subsequent systematic review assessing the utility of urine microscopy for differentiating prerenal AKI and ATN in hospitalized patients determined that the presence and number of RTE cells and RTE cell casts and/or granular casts in the urine sediment may be useful in predicting more severe kidney damage as reflected by nonrecovery of AKI or need for dialysis [54].

The Role of Novel Biomarkers

In more recent years, a number of investigational biomarkers have been studied with the goals of (i) detecting AKI at an earlier stage ("subclinical AKI" occurring prior to a rise in serum creatinine [SCr]); (ii) determining the location and severity of kidney injury; and (iii) predicting outcomes such as the development of CKD following AKI [55].

Urinary kidney injury molecule-1 (KIM-1) is a biomarker that has shown promise for both the early diagnosis of AKI and the differentiation of ATN from other etiologies of kidney disease. In one case-control study of 20 children who underwent cardiopulmonary bypass surgery with or without the subsequent development of AKI (defined as a >50% increase in SCr from baseline within 48 hours), urinary KIM-1 increased postoperatively only in those children who developed AKI [56]. In another study, normalized urinary KIM-1 levels were significantly higher in patients with biopsy-proven ATN compared to those with other forms of kidney disease.

The Translational Research Investigating Biomarkers and End Points for Acute Kidney Injury (TRIBE-AKI) consortium conducted a prospective, multicenter cohort study in adults undergoing cardiac surgery to assess whether postoperative measures of urine interleukin-18 (IL-18), urine neutrophil gelatinase-associated lipocalin (NGAL), or plasma NGAL could identify patients destined to develop AKI and other adverse outcomes. Results revealed that urine IL-18 and urine and plasma NGAL levels peaked

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within 6 hours after surgery. After multivariable adjustment, the highest quintiles of urine IL-18 and plasma NGAL were associated with 6.8-fold and 5-fold higher odds of AKI, respectively, compared with the lowest quintiles. Elevated urine IL-18 and urine and plasma NGAL levels associated with longer length of hospital stay, longer ICU stay, and higher risk for dialysis or death [57].

More recently, the multicenter Sapphire study discovered and validated two novel cell cycle arrest urine biomarkers for risk stratification of AKI, tissue inhibitor of metalloproteinases-2 (TIMP-2) and insulin-like growth factor-binding protein 7 (IGFBP7) [58]. The primary endpoint was Kidney Disease Improving Global Outcomes (KDIGO) stages 2 and 3 AKI within 12 hours of sample collection. The combination of TIMP-2 and IGFBP7 produced an area under the receiver operating characteristics curve (AUC) of 0.80, which was significantly superior to all previously described biomarkers for AKI. Additionally, risk for major adverse kidney events (death, need for renal replacement therapy [RRT], or persistent renal dysfunction) within 30 days elevated sharply for [TIMP-2]·[IGFBP7] above 0.3 $(ng/ml)^2/1000$ and doubled when values were >2.0 $(ng/ml)^2/1000$. Based in part on these observations, a point of care device measuring these two biomarkers was approved by the Food and Drug Administration (FDA) in 2014 to aid in the rapid and early identification of patients at high risk for developing AKI.

The above data clearly suggest potential value for next-generation biomarkers for both early diagnosis of and prognostication in AKI, however many questions remain about the best ways to apply these markers in clinical practice, and it remains to be seen whether early knowledge of risk of AKI will translate into improved clinical outcomes [55]. In addition, the sensitivity and specificity of these biomarkers for the specific diagnosis of ATN versus other forms of AKI is not yet determined. In this regard, a single-center trial examined the effect of a "KDIGO bundle" consisting of optimization of volume status and hemodynamics, avoidance of nephrotoxic drugs, and preventing hyperglycemia in high-risk patients defined by urinary [TIMP-2]·[IGFBP7] >0.3 $(ng/ml)^2/1000$ undergoing cardiac surgery. The primary endpoint was the rate of AKI defined by KDIGO criteria within the first 72 hours after surgery. AKI was significantly reduced with the intervention compared to controls (55.1 vs. 71.7%; ARR, 16.6%). The implementation of the bundle resulted in significantly improved hemodynamic parameters at different time points, less hyperglycemia, and use of ACE inhibitors/ARBs compared to controls. Rates of moderate to severe AKI were also significantly reduced by the intervention compared to controls. This promising study suggests that biomarker-guided interventions may be of benefit in decreasing the rate and progression of AKI [59].

Prognosis

Renal Recovery After ATN

The duration and outcome of ATN vary depending on the length and severity of the initial insult and the presence or absence of recurrent ischemia and/or repeated exposure to nephrotoxins [60, 61]. While the majority of patients return to or near their previous level of kidney function, recovery does not occur in all cases [62]. Progression from AKI to CKD and end-stage renal disease (ESRD) is an area of increasing interest and active research, largely focusing on understanding the mechanisms of injury and maladaptive repair after ATN with the goal of slowing or halting progression [63].

Schiffl and colleagues prospectively evaluated critically ill patients with normal baseline kidney function who developed clinically diagnosed severe ATN necessitating RRT. At discharge, 57% of the 226 surviving patients had normal kidney function, while 33% had mild to moderate renal failure (SCr 1.3–3 mg/dl), and 10% had severe renal failure (SCr 3–6 mg/dl). Multivariate analysis showed that neither patient characteristics (age, gender, comorbid conditions), severity of illness (APACHE III, number of failed organs), nor mode and duration of RRT were related to recovery of renal function. The authors concluded that, when critically ill patients with normal baseline kidney function survive the precipitating cause of ATN, the vast majority will recover sufficient renal function [62].

Not surprisingly, pre-existing CKD represents a major risk factor for the development of more severe AKI, greater need for RRT, and lower probability of renal recovery [64]. Additional risk factors for irreversible decline in kidney function include (i) older age; (ii) hypoalbuminemia; (iii) comorbidities including diabetes and heart failure; and (iv) more severe AKI requiring RRT [65, 66].

Mortality After ATN

Several studies have demonstrated an association between AKI during hospitalization and in-hospital and long-term mortality.

In the Acute Kidney Injury-Epidemiologic Prospective Investigation (AKI-EPI) study, a total of 1032 ICU patients out of 1802 total patients (57%) developed AKI by KDIGO criteria. Increasing AKI severity was associated with hospital mortality when adjusted for other variables (ORs: stage 1 = 1.679, stage 2 = 2.945, stage 3 = 6.884) [67].

Importantly, AKI has been shown to represent a risk factor for long-term mortality even in those patients who experience normalization of SCr after AKI. Bucaloiu and

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colleagues used a propensity score-matched cohort method to retrospectively evaluate the risk of death after reversible, hospital-associated AKI in patients with normal pre-hospital kidney function. Of patients alive at 90 days, 1610 patients with reversible AKI were matched with 3652 controls. At a median follow-up of just over 3 years, the risk of death associated with reversible AKI was significant (hazard ratio, 1.50) in Cox proportional hazard models. Adjustment for the development of CKD during follow-up attenuated but did eliminate this increased risk (hazard ratio 1.18). Based on this data, investigators concluded that a resolved episode of hospital-associated AKI has important implications for the longitudinal surveillance of patients [68].

Loss of Renal Reserve as a Predictor and Consequence of ATN

Renal functional reserve (RFR) can be used to measure the capacity of the kidney to increase GFR under conditions of physiologic stress and may serve as a functional marker that assesses susceptibility to injury. One method of measuring RFR is to measure changes in GFR in response to a high-protein meal. In a recent study, preoperative RFR was lower in patients who experienced AKI and predicted AKI with an AUC of 0.83. Patients with preoperative RFRs not greater than 15 ml/min/1.73m^2, despite normal resting GFRs, were 11.8 times more likely to experience AKI [69]. Thus, measurement of RFR preoperatively may identify patients who are likely to benefit from preventive measures or to select for use of biomarkers for early detection. In a follow-up to this study, AKI patients displayed a significant decrease in RFR (from 14.4 to 9.1 ml/min/1.73 m^2) and patients without AKI but with positive postoperative cell-cycle arrest biomarkers also experienced a similar decrease of RFR (from 26.7 to 19.7 ml/min/1.73m^2). In contrast, patients with neither clinical AKI nor positive biomarkers had no such decrease of RFR. Thus, AKI, and even AKI defined by biomarkers (but not elevations in SCr), is associated with persistent falls in RFR and highlights the long-term deleterious effects of this occurrence [70]. Further studies are needed in this area.

Prevention

Many studies have been performed to determine if any approaches can minimize the risk of ATN when patients are faced with a high-risk clinical scenario, such as sepsis, major surgery, or the need for certain antibiotics or iodinated radiocontrast dye. This section seeks to review the studies currently available that guide best practice and inform our evidence-based recommendations for the prevention of ATN. An exhaustive list of the various compounds and strategies that have been reported is beyond the scope of this chapter. Thus, representative examples are discussed and other compounds and strategies are listed in Tables 10.2 and 10.3.

Avoiding Nephrotoxic Medications and Mitigating Risk of ATN

Aminoglycosides

Aminoglycosides remain important therapies for the management of life-threatening gram-negative infections [48]. Nephrotoxicity represents the major dose-limiting toxicity of these drugs, occurring in approximately 10–25% of patients [119–123]. Toxicity is mediated primarily by damage to PT cells, impairing tubular reabsorption and compromising cell viability [124].

More than 60 trials have been conducted to evaluate the benefits of altering the dosing schedule of aminoglycosides, with the goal of limiting uptake by PT cells. Blaser and König evaluated the results of 24 randomized clinical trials including 3181 patients comparing once-daily versus multiple-daily dosing regimens for amikacin, netilmicin, and gentamicin. Analysis revealed superior results for once-daily regimens with respect to clinical and bacteriological efficacy. While nephrotoxicity occurred less frequently with once-daily dosing (4.5% vs. 5.5%), results did not reach statistical significance [72]. In another meta-analysis of similar size, Barza et al. demonstrated a reduction in nephrotoxicity with once-daily dosing, but no difference in patient mortality [73]. Hatala et al. evaluated 13 studies and revealed a trend toward reduced nephrotoxicity with once-daily dosing that did not reach statistical significance, while Ferriols-Lisart and Alós-Almiñana analyzed 18 studies including 2317 patients and demonstrated a reduction in summary odds of nephrotoxicity with once-daily aminoglycoside dosing [74, 75]. Two additional meta-analyses by Munckhof et al. and Ali and Goetz failed to show a significant difference in the rates of kidney injury [71, 76].

The cumulative conclusions of these analyses indicate that once-daily dosing strategies generally lead to less AKI when compared with multiple-dose strategies, though the benefits of this approach are modest [125].

Amphotericin B

Amphotericin B remains an important antifungal therapy. Unfortunately, nephrotoxicity is common and may occur in close to 25% of patients receiving conventional (nonlipid-based) formulations [126, 127]. Renal toxicity may take the form of renal tubular acidosis, impaired renal concentrating

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Table 10.2 Prevention of acute tubular necrosis in select high-risk settings.

Risk setting	Select key studies	Results of studies	Recommendation	Certainty of evidence	Strength of recommendation
Aminoglycosides	Ali and Goetz [71] (M)	No significant difference in the incidence of nephrotoxicity with SDD vs. MDD	We suggest that, in patients with normal kidney function in steady state, aminoglycosides be administered in a single daily dose rather than multiple daily doses. We also recommend that, for patients with CKD stage 3b and later, aminoglycosides be avoided unless there are no other alternatives.	Moderate	Strong
	Blaser and König [72] (M)	Trend toward decreased nephrotoxicity with SDD vs. MDD (4.5% vs. 5.5%); did not reach statistical significance			
	Barza et al. [73] (M)	Reduced risk of nephrotoxicity with SDD vs. MDD			
	Ferriols-Lisart and Alós-Almiñana [74] (M)	Reduced summary odds of nephrotoxicity with SDD vs. MDD			
	Hatala et al. [75] (M)	Trend toward decreased nephrotoxicity with SDD vs. MDD; did not reach statistical significance			
	Munckhof et al. [76] (M)	No significant difference in the incidence of nephrotoxicity with SDD vs. MDD			
Amphotericin B	Anderson [77] (M)	Supplementing dietary sodium chloride intake with 150 mEq intravenously or orally before or at time of drug administration "will likely prevent much of the observed nephrotoxicity" associated with amphotericin B	We recommend the administration of a saline load (1 l of 0.9% sodium chloride IV) prior to amphotericin B administration.	Moderate	Strong
	Llanos et al. [78] (RCT)	Creatinine clearance decreased in patients pretreated with dextrose in water, but remained unchanged in patients pretreated with 0.9% saline			
	Botero Aguirre and Restrepo Hamid [79] (Cochrane systematic review)	Significantly lower risk of nephrotoxicity with liposomal amphotericin B vs. conventional amphotericin B deoxycholate	We suggest using lipid formulations of amphotericin B rather than conventional formulations of amphotericin B except in circumstances were the efficacy of conventional formulations may be greater.	Moderate	Strong
Vancomycin + piperacillin-tazobactam	Chen et al. [80] (M)	Increased risk of AKI with concurrent use of vancomycin + piperacillin-tazobactam vs. vancomycin + other β-lactam	We recommend using piperacillin-tazobactam cautiously in those patients receiving vancomycin. Use should be limited to those who have appropriate indications. Alternative antibiotics should be considered whenever possible.	Moderate	Strong
	Giuliano et al. [81] (M)	Increased risk of AKI with vancomycin + piperacillin-tazobactam vs. vancomycin ± other β-lactam			
	Hammond et al. [82] (M)	Increased risk of AKI with concomitant vancomycin + piperacillin-tazobactam vs. vancomycin without piperacillin-tazobactam			
	Luther et al. [83] (M)	Increased odds of AKI with vancomycin + piperacillin-tazobactam vs. vancomycin monotherapy, vancomycin +cefepime or carbapenem, and piperacillin-monotherapy; NNH = 11			
	Mellen et al. [84] (M)	Increase in the incidence of nephrotoxicity with vancomycin + piperacillin-tazobactam vs. vancomycin alone or in combination with cefepime or meropenem			

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Iodinated radiocontrast dye[a]	Brar et al. [85] (RCT)	Decrease in CIN with LVEDP-guided 0.9% saline volume expansion vs. standard hydration group (6.7% vs. 16.3%) in patients undergoing cardiac catheterization	We recommend IV volume expansion for patients at risk for CIN without contraindications to volume expansion.	Moderate	Strong
	Jurado-Román [86] et al. (RCT)	Decreased incidence of CIN with 0.9% saline vs. no hydration in the setting of emergent PCI for STEMI (11% vs. 21%)			
	Luo et al. [87] (RCT)	Lower rate of CIN with 0.9% saline vs. no hydration after PCI for STEMI (20.4% vs. 35.2%)			
	Nijssen EC et al. [88] (RCT)	No difference in rate of CIN between 0.9% saline and no prophylaxis (2.6% vs. 2.7%); not an especially high-risk group (low rate of CIN, 65% had only mild CKD with eGFR 45–59 ml/min/1.73m^2, only 48% received intra-arterial contrast)			
	Trivedi et al. [89] (RCT)	Decreased risk of CIN 0.9% saline vs. unrestricted oral intake (1/27 vs. 9/26 patients)			
	Weisbord et al. [90] (RCT)	No significant difference in primary endpoint (composite of death, need for RRT, or persistent decline in kidney function at 90 days) or CIN with IV 1.26% BIC vs. 0.9% saline	We do not recommend the routine use of sodium bicarbonate solution over NS for the prevention of CIN.	Strong	Strong
	Zoungas et al. [91] (M)	Lower pooled risk of CIN with BIC (RR, 0.62); significant heterogeneity; small, poor-quality studies more likely to suggest benefit; no clear effects on risk of RRT, heart failure, or mortality			
	Weisbord et al. [90] (RCT)	No significant difference in primary endpoint (composite of death, need for RRT, or persistent decline in kidney function at 90 days) or CIN with PO NAC vs. placebo	We do not recommend the routine use of N-acetylcysteine for the prevention of CIN.	Strong	Strong
Rhabdomyolysis	Gunal et al. [92] (case series)	16 crush injury victims; time between rescue and initiation of IVF significantly longer in victims requiring RRT	We recommend early and aggressive hydration in all patients with rhabdomyolysis with CK values >5000 U/l or increasing CK values in the absence of volume overload.	Moderate	Strong
	Ron et al. [93] (case series)	7 patients with crush injury treated immediately with alkaline solute diuresis on extraction; no patient developed ARF (attributed to prompt administration of IVF)			
	Brown et al. [94] (retrospective chart review)	No difference in rates of ARF, dialysis, or mortality with BIC/MAN vs. without BIC/MAN among patients with CK >5000 U/l; trend toward improved outcome in subgroup with CK >30 000 U/l	We do not recommend the routine use of mannitol to prevent or treat rhabdomyolysis given the risks of volume depletion and hypernatremia, and conflicting evidence regarding potential benefit.	Low	Weak
	Kim et al. [95] (RCT)	Significant difference in incidence of rhabdomyolysis (CK >5000 U/l) with early urine alkalization group vs. hydration alone in patients admitted with doxylamine overdose	Use of bicarbonate-based fluids to prevent or treat rhabdomyolysis may be considered in patients in whom a diuresis has been established with 0.9% saline. Bicarbonate infusion should be discontinued and isotonic saline resumed for arterial pH ≥7.5, serum bicarbonate >30 mEq/l, or if symptomatic hypocalcemia develops.		
	Scharman and Troutman [96] (systematic literature review)	27 studies; 3 studies concluded no significant difference in rates of ARF with BIC vs. no BIC; no evidence supported a preferred fluid type; interpretation limited by lack of controlled trials and heterogeneity			

(*Continued*)

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Table 10.2 (Continued)

Risk setting	Select key studies	Results of studies	Recommendation	Certainty of evidence	Strength of recommendation
Surgery (all types)	Zacharias et al. [97] (Cochrane systematic review)	Investigated preventative strategies including dopamine and its analogues, diuretics, CCBs, ACE inhibitors, NAC, ANP, and erythropoietin; no group showed a significant change in mortality or kidney injury in treatment groups vs. controls	We do not recommend the routine use of these interventions for the prevention of AKI/ATN in the perioperative setting.	Very low	Weak
Cardiac surgery	Lamy et al. [98] (RCT)	Lower rate of AKI at 30 d with off-pump vs. on-pump CABG; no difference in renal failure requiring RRT or death; increased risk of early revascularization	We suggest that off-pump coronary artery bypass graft surgery not be selected solely for the purpose of reducing perioperative AKI.	Low	Weak
	Nigwekar et al. [99] (M)	Reduction in overall AKI (OR, 0.57) and AKI requiring RRT (OR, 0.55) with off-pump vs. on-pump CABG; limited by lack of uniform definition for AKI and heterogeneity			
	Seabra et al. [100] (M)	Significant 40% lower odds of postoperative AKI and a nonsignificant 33% lower odds of need for RRT compared with off-pump vs. on-pump CABG			

[a] For a more detailed discussion of the prevention and treatment of CIN, please see Chapter 11 on contrast-induced nephropathy.
ACE, angiotensin-converting-enzyme; AKI, acute kidney injury; ANP, atrial natriuretic peptide; ARF, acute renal failure; ATN, acute tubular necrosis; BIC, sodium bicarbonate; BIC/MAN, sodium bicarbonate + mannitol; CABG, coronary artery bypass graft; CCB, calcium channel blocker; CIN, contrast-induced nephropathy; CK, creatine kinase; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate, IV, intravenous, IVF, intravenous fluid; LVEDP, left ventricular end-diastolic pressure; M, meta-analysis; MDD, multiple daily dosing; NAC, *N*-acetylcysteine; NNH, number needed to harm; NS, normal saline; OR, odds ratio; PCI, percutaneous coronary intervention; RCT, randomized controlled trial; RR, relative risk; RRT, renal replacement therapy; SCr, serum creatinine; SDD, single daily dosing; STEMI, ST elevation myocardial infarction.

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Table 10.3 Select agents investigated for the prevention of acute tubular necrosis.

Agent or procedure for prevention of ATN	Select key studies	Results of studies	Recommendation	Certainty of evidence	Strength of recommendation
Dopamine	Bellomo et al. [101] (RCT)	No significant difference in renal function, need for RRT, ICU or hospital length of stay, or mortality in critically ill patients with early renal dysfunction receiving low-dose dopamine (2 mcg/kg/min) vs. placebo	In the absence of convincing evidence of benefit, and in light of potential risks, we do not recommend the routine use of dopamine for prevention of AKI.	High	Strong
	Friedrich et al. [102] (M)	Increased urine output and improvement in SCr on day 1 with low-dose dopamine (≤5 mcg/kg/min); no sustained improvement in renal function, decrease in need for RRT, or decrease in mortality (did not separate prophylactic from therapeutic trials)			
	Kellum and Decker [103] (M)	No significant benefit of low-dose dopamine (<5 mcg/kg/min) for prevention of AKI			
Fenoldopam	Bove et al. [104] (RCT)	Similar rates of AKI with the use of fenoldopam vs. dopamine in high-risk patients following induction of anesthesia for cardiac surgery	In the absence of high-quality adequately powered trials and consistent data demonstrating improvement in patient-centered outcomes, and in light of the risk of hypotension, we suggest not using fenoldopam to prevent ischemic ATN.	Low	Weak
	Gillies et al. [105] (M)	Reduction in risk of AKI in patients receiving fenoldopam vs. placebo; no difference in mortality or need for RRT; high risk of bias in 5/6 studies			
	Landoni et al. [106] (M)	Lower risk of AKI in fenoldopam-treated patients vs. placebo or other therapy (primarily low-dose dopamine); no significant increase in complications; heterogeneous populations; 6 studies lacked placebo controls			
	Morelli et al. [107] (RCT)	Lower rate of AKI (increase in SCr above 1.7 mg/dl) in patients treated with prophylactic fenoldopam vs. placebo; no significant difference in rate of severe acute renal failure (SCr >3.4 mg/dl)			
Loop diuretics	Bove et al. [108] (M)	Significant improvement in survival in patients treated with preventative furosemide bolus(es) vs. any comparator (standard care, 0.9% saline, 0.9% saline ± mannitol, or furosemide infusion)	We do not recommend the routine use of loop diuretics for the prevention of ATN.	Moderate	Strong
	Hager et al. [109] (RCT)	No significant difference in post-operative decline in creatinine clearance between low-dose furosemide (1 mg/h) and placebo groups; increased incidence of hypokalemia with use of furosemide			
	Ho et al. [110] (M)	No significant difference in in-hospital mortality or need for RRT with the use of furosemide to prevent acute renal failure			
	Ho et al. [111] (M)				
	Lassnigg et al. [112] (RCT)	Increased rate of AKI in patients randomized to receive furosemide (0.5 mcg/kg/min) vs. 0.9% saline or low-dose dopamine			

(*Continued*)

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Table 10.3 (Continued)

Agent or procedure for prevention of ATN	Select key studies	Results of studies	Recommendation	Certainty of evidence	Strength of recommendation
Natriuretic peptides	Nigwekar et al. [113] (Cochrane systematic review)	Decreased need for RRT but no difference in mortality in patients receiving prophylactic low-dose ANP compared to high-dose ANP or controls; authors acknowledged paucity of high-quality, adequately powered data	In the absence of high-quality adequately powered trials, and in light of the risk of hypotension, we suggest not using natriuretic peptides to prevent ischemic ATN.	Low	Weak
	Nigwekar et al. [114] (M)	Natriuretic peptide administration (ANP, BMP, urodilantin) was associated with a reduction in need for RRT and a nonsignificant trend toward reduction in 30 days or in-hospital mortality; most studies were small and lacked adequate power to reach statistical significance on their own			
Remote ischemic preconditioning	Menting et al. [115] (Cochrane systematic review)	RIPC by cuff inflation made little or no difference in SCr (postoperative days 1–3), need for dialysis, length of hospital stay, or all-cause mortality compared with no RIPC prior to surgery (renal transplant excluded)	In the absence of clear benefit, we do not recommend the routine use of RIPC for the prevention of ischemic ATN.	High	Strong
Statins[a]	Billings et al. [116] (RCT)	No reduction in the risk of AKI (0.3 mg/dl increase in SCr within 48 hours) in patients undergoing cardiac surgery with use of high-dose atorvastatin vs. placebo; increased AKI among statin-naïve CKD patients	In the absence of clear benefit, we do not recommend the routine use of statins for the prevention of ischemic ATN.	High	Strong
	Park et al. [117] (RCT)	Acute perioperative atorvastatin use not associated with lower incidence of AKI (AKIN criteria) or improved clinical outcomes after valvular heart surgery compared with placebo			
	Prowle et al. (RCT) [118]	Short-term perioperative atorvastatin use not associated with reduction in AKI (RIFLE R or greater) or smaller increases in urinary NGAL			

[a] For a discussion of statin administration as it pertains to the use of iodinated radiocontrast dye, please see Chapter 11 on contrast-induced nephropathy.
AKI, acute kidney injury; AKIN, Acute Kidney Injury Network; ANP, atrial natriuretic peptide; ATN, acute tubular necrosis; BNP, brain natriuretic peptide; CKD, chronic kidney disease; ICU, intensive care unit; NGAL, neutrophil gelatinase-associated lipocalin; M, meta-analysis; RCT, randomized controlled trial; RIFLE, Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease criteria; RIPC, remote ischemic preconditioning; RRT, renal replacement therapy; SCr, serum creatinine concentration.

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ability, electrolyte abnormalities (hypokalemia, sodium, and magnesium wasting), and ATN [128]. In attempts to minimize kidney injury, several preventative strategies have been investigated, including salt loading (volume expansion) and the use of lipid-based formulations.

Volume Expansion (Salt Loading) In response to animal data suggesting that enhanced TGF contributes to the nephrotoxicity of amphotericin B, a number of studies have evaluated the utility of salt loading through saline infusion with the goal of decreasing sensitivity to TGF and preserving GFR [129].

In 1995, Anderson published a meta-analysis of the five available human studies investigating the role of salt loading. He concluded that 150 mEq of sodium chloride daily intravenously or orally will likely prevent much of the observed nephrotoxicity and should be carried out routinely [77]. Anderson's conclusions were based largely on one placebo-controlled trial, in which patients treated with thrice-weekly amphotericin for leishmaniasis were randomized to receive either 1 l of 0.9% saline or 1 l of 5% dextrose in water immediately prior to each amphotericin B dose [48]. Results showed a reduction in creatinine clearance in the control group compared with patients in the saline group ($P < 0.05$). None of the patients sustained an increase in SCr to values greater than 1.7 mg/dl [78].

There has been minimal recent research in this area, and it is unlikely that any randomized trials will be conducted due to practical and ethical considerations. While the data above is clearly limited, there appears to be minimal harm in giving patients a saline load (1 l of 0.9% sodium chloride intravenously) prior to amphotericin B administration, and this should be considered the standard of care.

Use of Lipid-Based Amphotericin B Formulations Several animal and human studies suggest that lipid-based formulations of amphotericin B (either lipid complex or liposomal) may decrease the incidence and severity of kidney injury.

In a recent systematic Cochrane review, 10 randomized controlled trials (RCTs) comparing amphotericin B sodium deoxycholate with liposomal amphotericin B were meta-analyzed. The liposomal formulation was found to be significantly safer in terms of nephrotoxicity, defined as a ≥2-fold increase in SCr from baseline (RR, 0.49). The sensitivity analysis performed did not change the significance of difference in favor of the liposomal formulation, and the overall certainty of evidence was determined to be moderate based on GRADE Working Group criteria [79].

Vancomycin and Piperacillin-Tazobactam

Vancomycin is a known cause of nephrotoxic ATN, with incidence of AKI ranging from 5% to 43% depending on the population studied [130–132]. Risk factors include vancomycin exposure (trough levels 15 mg/l or higher, larger AUC, longer duration of therapy), host susceptibility to vancomycin (increased body weight, pre-existing kidney dysfunction, critical illness), and concurrent nephrotoxin therapy [130].

Since 2011, multiple studies have demonstrated an increased risk of AKI with the use of vancomycin in combination with piperacillin-tazobactam, and five meta-analyses have been conducted to investigate this proposed increased risk [80–84]. Giuliano et al. evaluated 15 observational cohort studies including a total of 3258 patients and documented an association with the development of AKI with vancomycin + piperacillin-tazobactam compared with vancomycin ± beta-lactam (OR, 3.649) [81]. Additional studies have demonstrated similar findings [80, 82, 84]. In the largest meta-analysis, the overall occurrence rate of AKI was 22.2% for the vancomycin + piperacillin-tazobactam group compared with 12.9% for the comparator groups (vancomycin monotherapy, vancomycin + cefepime or carbapenem, piperacillin monotherapy), yielding an overall number needed to harm of 11 [83].

Taken together, these studies provide compelling evidence supporting an increased risk for AKI in those patients treated with vancomycin and piperacillin-tazobactam. This combination should be initiated cautiously and only in patients with appropriate indications for use.

Iodinated Radiocontrast Dye

Iodinated radiocontrast dye is a common cause of ATN, with incidence of contrast-induced nephropathy (CIN) reported to be as high as 15–25% (depending on the exact definition and agent used) in certain high-risk populations receiving intra-arterial injections [133–135]. These include patients with pre-existing renal impairment or certain risk factors such as diabetes, congestive heart failure, or concurrent administration of nephrotoxic medication [125, 136, 137]. A number of measures (hydration, types of contrast, and medications) have been investigated in attempts to prevent CIN [137]. Of these, the most critical appears to be optimization of volume status, and we recommend the administration of isotonic fluids prior to and for several hours after the administration of iodinated contrast in at-risk patients without contraindications to volume expansion (see Table 10.2) [125]. For a detailed discussion of the pathophysiology, prevention, and treatment of contrast-induced AKI, see Chapter 11 [Weisbord and Gallagher].

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Treatment

Many drug classes and strategies have been studied as potential treatments for established ATN, and several representative examples are outlined in Table 10.4. Unfortunately, the results of these investigations have been largely disappointing. Because no single effective treatment for ATN has been identified, the mainstays of therapy remain appreciation of AKI risk, early detection of injury, initiation of appropriate supportive care, and avoidance of further harm [154]. Treatment priorities must include (i) discontinuation of nephrotoxic medications whenever possible; (ii) optimization of hemodynamics and RBF; (iii) attention to volume management with caution to avoid both hypovolemia and fluid overload; (iv) correction of electrolyte and acid-base derangements; and (v) timely initiation of RRT in appropriately selected patients.

Discontinuation of Nephrotoxic Medications

All patients with established ATN require a thorough review of their medications. Nephrotoxic drugs (NSAIDs, ACE inhibitors, ARBs, aminoglycosides) and agents such as iodinated radiocontrast dye should be avoided or stopped, if possible. Additionally, medication doses should be adjusted to account for reduced renal clearance.

Optimization of Hemodynamics and RBF and Volume Management

Early measures to treat established ATN must include optimization of cardiac output and maintenance of hemodynamics to ensure adequate systemic perfusion and RBF; the specific approach will vary based on patient factors and the clinical scenario (hypovolemic shock, tumor lysis syndrome, heart failure) [2].

Close attention must be paid to volume status. While volume depletion should be corrected when present, there is a growing body of evidence documenting poorer patient outcomes with excessive fluid administration. In the Fluid and Catheter Treatment Trial (FACTT), a conservative fluid strategy (achieved through the protocolized use of furosemide to target low central venous pressure or pulmonary capillary wedge pressure) was associated with decreased ICU length of stay and decreased length of mechanical ventilation in patients with acute lung injury without an increase in nonpulmonary-organ failures or need for dialysis [155]. Additionally, a positive fluid balance at 72 hours post-admission has been shown to be associated with increased mortality, and some data suggest that a positive fluid balance as early as 12 hours may be associated with increased risk of death [156–159].

An association between positive fluid balance and mortality has been demonstrated in patients with established AKI [142, 145]. In a secondary analysis of AKI patients from a multicenter, prospective cohort study in 10 Italian ICUs, higher mean fluid balance was associated with greater mortality, and diuretic use was associated with better survival in this population (adjusted HR, 0.25) [145]. Using data from the FACTT, 306 AKI patients were identified and included in a post hoc analysis. Grams et al. showed that post-AKI fluid balance was significantly associated with 60-day mortality in both crude and adjusted analysis, and that higher post-AKI furosemide doses had a protective effect on mortality but no significant effect after adjustment for post-AKI fluid balance [142]. While the data does not support the routine use of diuretics in euvolemic patients with established ATN (who may develop volume depletion and subsequent worsening of ischemic kidney injury), diuretics and/or RRT may be considered in those with evidence of volume overload. For a review of relevant studies investigating the role of loop diuretics in the treatment of ATN, see Table 10.4.

Correction of Electrolyte and Acid-Base Disturbances and Timely Initiation of RRT

Metabolic derangements seen in established ATN include hyperkalemia, hyponatremia, hyperphosphatemia, and acidemia, and these may range in severity from mild to life-threatening. Rapid rises in serum potassium concentration, as may occur in the presence of oliguria and tissue breakdown (rhabdomyolysis, tumor lysis syndrome), are especially worrisome. In these cases, emergency treatment may be required.

Despite extensive research, debate continues regarding the optimal timing, modality, and dosing of RRT in ATN. The KDIGO Clinical Practice Guideline for AKI suggests initiation of RRT emergently when life-threatening changes in fluid, electrolyte, and acid-base balance exist. In the absence of emergent indications, KDIGO suggests that clinicians consider the broader clinical context, the presence of conditions that can be modified with RRT, and trends in laboratory results when making the decision to start RRT (recommendations not graded) [125].

Conclusions

ATN is a common clinical problem associated with increased risk of CKD and mortality. Unfortunately, while several classes of agents have been investigated, thus far no specific pharmacologic strategies have proven effective for

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Table 10.4 Select agents investigated for the treatment of established acute tubular necrosis.

Agent or procedure for treatment of AKI	Select key studies	Results of studies	Recommendation	Certainty of evidence	Strength of recommendation
Alkaline phosphatase	Pickkers et al. [138] (RCT)	No significant improvement in short-term (7 days) creatinine clearance with human recombinant AP (vs. placebo) in critically ill patients with sepsis-associated AKI	In the absence of data demonstrating consistent improvement in patient-centered outcomes, we suggest not using alkaline phosphatase for the treatment of AKI.	Moderate	Strong
	Pickkers et al. [139] (RCT)	Significant ($P = 0.02$) difference in favor of AP relative to controls for the primary endpoint (progress in renal outcome variables as measured by ECC and requirement and duration of RRT) at 28 days; ECC 50 ± 27 to 108 ± 73 ml/min (mean ± SEM) in AP group vs. 40 ± 37 to 65 ± 30 ml/min for placebo ($P = 0.01$); reductions in RRT requirement and duration did not reach statistical significance			
Dopamine	Friedrich et al. [102] (M)	Increased urine output and improvement in SCr on day 1 with low-dose dopamine (≤5 mcg/kg/min); no sustained improvement in renal function, decrease in need for RRT, or decrease in mortality (did not separate prophylactic from therapeutic trials)	In the absence of convincing evidence of benefit, and in light of potential risks, we do not recommend the use of dopamine for the treatment of AKI.	High	Strong
	Kellum and Decker [103] (M)	No significant benefit of low-dose dopamine (<5 mcg/kg/min) for treatment of AKI			
	Lauschke et al. [140] (RCT)	Increase in renal vascular resistance with low-dose dopamine (2 mcg/kg/min) in patients with ARF (vs. decrease in renal vascular resistance without ARF); concern for worsening of renal perfusion in dopamine-treated patients			
Loop diuretics	Cantarovich et al. [141] (RCT)	No difference in survival or rate of renal recovery with high dose furosemide (25 mg/kg/d IV or 35 mg/kg/d PO) vs. placebo; increased UOP in furosemide group without reduction in number of treatments or time on dialysis	We suggest not using diuretics to treat AKI, except in the management of volume overload.	Moderate	Weak
	Grams et al. [142](RTC, post hoc analysis)	Higher post-AKI fluid balance associated with increased 60-day mortality; higher post-AKI furosemide associated with improved survival (no significant effect after adjustment for post-AKI fluid balance)			
	Mehta et al. [143] (retrospective cohort study)	Increased risk of death and nonrecovery renal function with use of furosemide, bumetanide, metolazone, and/or hydrodiuril vs. no diuretics			
	Shilliday et al. [144] (RCT)	Randomized to receive torsemide, furosemide, or placebo in addition to dopamine and mannitol; no decrease in rate of renal recovery, need for RRT, or death with diuretics despite increased UOP			
	Teixeira et al. [145] (prospective cohort study, secondary analysis)	Higher MFB in nonsurviving AKI patients vs. surviving AKI patients; higher MFB independently associated with 28-day mortality; diuretic use associated with better survival in patients with higher MFB and lower MUV			
	Uchino et al. [146] (prospective cohort study)	No significant difference in patient mortality associated with the use of diuretics (almost exclusively furosemide) vs. no diuretics in critically ill ICU patients			

(*Continued*)

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Table 10.4 (Continued)

Agent or procedure for treatment of AKI	Select key studies	Results of studies	Recommendation	Certainty of evidence	Strength of recommendation
Fenoldopam	Brienza et al. [147] (RCT)	Randomized to receive fenoldopam (0.1 mcg/kg/min) or dopamine; lower SCr in fenoldopam group after 4-day infusion (change from baseline, −0.041 vs. -0.09 mg/dl, $P = 0.02$); no decrease in need for RRT	In the absence of data demonstrating consistent improvement in patient-centered outcomes, and in light of the risk of hypotension, we suggest not using fenoldopam for the treatment of established ischemic ATN.	Low	Weak
	Bove et al. [148] (RCT)	No difference in need for RRT or 30-day mortality with fenoldopam vs. placebo; significantly more hypotension in fenoldopam group (26% vs. 15%, $P = 0.001$); stopped early for futility			
	Tumlin et al. [149] (RCT)	Trend toward lower 21-day mortality and decreased need for RRT with fenoldopam vs. placebo, but not statistically significant (underpowered, 11% absolute risk reduction)			
Insulin-like growth factor-1	Hirschberg et al. [150] (RCT)	In patients with sepsis and hypotension or hemodynamic shock, no differences noted in changes in GFR, urine output, need for RRT, or mortality with IGF-1 vs. placebo (mean treatment period 10.6 days)	In the absence of data from high-quality trials demonstrating improvement in patient-centered outcomes, we do not recommend the routine use of IGF-1 for the treatment of established AKI.	Moderate	Strong
Natriuretic peptides	Allgren et al. [151] (RCT)	No significant difference in overall dialysis-free survival at 21 days with anaritide (0.2 mcg/kg/min) vs. placebo; improved dialysis-free survival in subgroup with oliguria receiving anaritide; increased incidence of hypotension in anaritide group (46% vs. 18%, $P = 0.001$)	In the absence of data demonstrating consistent benefit in patient-centered outcomes, and in light of the risk of hypotension, we suggest not using ANP to treat ATN.	Moderate	Weak
	Lewis et al. [152] (RCT)	No statistically significant difference in dialysis-free survival or mortality with anaritide (0.2 mcg/kg/min) vs. placebo; greater incidence of hypotension (SBP <90) in the anaritide-treated group (95% vs. 55%, $P < 0.001$)			
	Nigwekar et al. [110] (Cochrane systematic review)	No difference in mortality with either low- or high-dose ANP; low-dose ANP associated with reduction in need for RRT; high-dose ANP associated with more adverse events (hypotension, arrhythmias); authors acknowledge paucity of high-quality, adequately powered data			
	Swärd et al. [153] (RCT)	61 postoperative patients with heart failure and AKI (not ischemic ATN) randomized to h-ANP (50 ng/kg/min) or placebo; decreased need for RRT and improved dialysis-free survival in h-ANP group vs. placebo; no significant difference in incidence of hypotension			

AKI, acute kidney injury; ANP, atrial natriuretic peptide; AP, alkaline phosphatase; ARF, acute renal failure; ATN, acute tubular necrosis; ECC, endogenous creatinine clearance; GFR, glomerular filtration rate; h-ANP, human atrial natriuretic peptide; ICU, intensive care unit; IGF-1, insulin-like growth factor-1; IV, intravenous; M, meta-analysis; MFB, mean fluid balance; MUV, mean urine volume; PO by mouth, RCT, randomized controlled trial; RRT, renal replacement therapy; SEM; standard error of the mean; SBP, systolic blood pressure; UOP, urine output.

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preventing or treating this condition. Thus, the approach to ATN centers on identifying patients at increased risk, minimizing ischemic and toxic exposures, early detection of kidney injury, and aggressive supportive care, including the maintenance of adequate hemodynamics and management of electrolyte and acid-base derangements.

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11

Iodinated Contrast and Acute Kidney Injury

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Acute kidney injury (AKI) is a widely recognized complication of intravascular administration of iodinated contrast media. The pathophysiology of contrast-associated acute kidney injury (CA-AKI) is thought to be related to hemodynamic perturbations in the kidney from contrast, direct toxic effects of contrast on tubular epithelial cells, and the generation of reactive oxygen species following contrast administration. While typically defined by small increments in serum creatinine within several days following contrast administration, the incidence of CA-AKI varies based on the precise definition employed, clinical characteristics of the patient population, and nature of the procedure being performed. The primary patient-related risk factor for CA-AKI is underlying kidney impairment, while absolute and effective circulating volume also increases risk. A multitude of studies have demonstrated that CA-AKI is associated with serious adverse short- and long-term outcomes, including death. However, it is currently unknown whether these associations are causal. This is important as a growing number of studies suggest that patients with chronic kidney disease (CKD), who are elevated risk for CA-AKI, are less likely to undergo indicated contrast-enhanced procedures such as coronary angiography compared with patients without CKD, likely out of fear by providers of precipitating CA-AKI. As CA-AKI is a potentially preventable form of renal injury, there has been substantial effort to identify interventions to reduce risk. Studies over the past several decades inform the current evidence basis for the prevention of this condition. Understanding the data that inform the current evidence basis for prevention is essential to minimize the burden of AKI related to contrast and to enhance the appropriate implementation of clinically indicated contrast-enhanced procedures in patients at risk for this iatrogenic condition.

Pathophysiology

The potential harms of the intravascular administration of radiological, iodine-based contrast media have been appreciated for over 60 years, with the recognized risk of AKI well described since the 1970s [1]. A series of pathophysiological processes likely underlie the development of contrast-induced CKI (Figure 11.1). After iodinated contrast is administered into the systemic circulation, blood flow to the outer renal medulla decreases while active transport and oxygen requirements in the distal nephron increase.

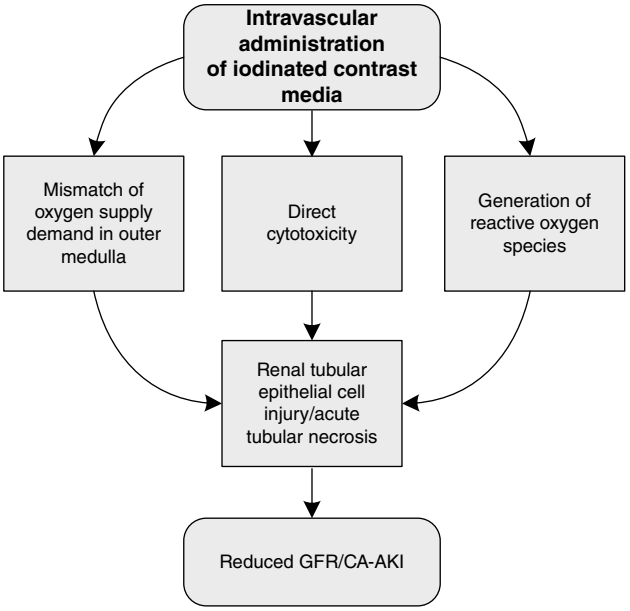

Figure 11.1 Potential processes underlying the pathophysiology of CA-AKI.

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The resulting mismatch in oxygen supply and demand in an anatomical portion of the kidney with low baseline oxygen reserve leads to ischemia of tubular epithelial cells [2, 3]. Further epithelial cell injury results from both the direct toxicity of the filtered iodinated contrast and the generation of injurious reactive oxygen species [4–9]. After being filtered at the glomerulus, iodinated contrast enters the tubular lumen where it has been shown to have cytotoxic effects that result in tubular epithelial cell necrosis [6–8, 10]. Contrast administration also leads to increased production of oxygen free radicals in the kidney that further contribute to epithelial and endothelial cell injury [11–17]. The cumulative result of these effects is acute tubular necrosis and an abrupt decline in kidney function.

Nomenclature and Definition

Historically, AKI following the administration of iodinated contrast media was referred to as contrast nephropathy or contrast-induced nephropathy. More recently, the Kidney Disease Improving Global Outcomes (KDIGO) organization proposed the term contrast-induced AKI [18, 19]. However, in many patients, other factors along with contrast administration likely contribute to the observed decline in kidney function. Consequently, contrast-associated AKI (CA-AKI) may be a more appropriate term. CA-AKI has commonly been defined by an increment in serum creatinine of ≥0.5 mg/dl or ≥25% within 48–72 hours of contrast administration. While this definition is highly sensitive, it has poor specificity for contrast-induced damage as multiple other factors, including fluid shifts, medications, and atheroembolic disease can cause an increase in serum creatinine, with or without underlying kidney injury, independent of the effect of contrast. Nonetheless, this continues to be among the most commonly used definitions of this condition. In keeping with efforts to establish a unifying definition of AKI that is independent of etiology, CA-AKI has also been defined based on an increase in serum creatinine of ≥0.3 mg/dl within 48 hours [18]. However, this definition also has poor specificity. In light of the issues associated with defining a condition based on nominal increments in a biological parameter (i.e. serum creatinine) that is not specific for kidney injury, efforts to identify other biomarkers that better define and more accurately predict the prognosis of CA-AKI are needed.

Incidence

The reported incidence of CA-AKI has varied across studies due to differences in patient characteristics and procedural variables, as well as the criteria employed to define the development of AKI. Weisbord et al. demonstrated that CA-AKI, defined by an increase in serum creatinine of ≥25%, developed in 13.2%, 8.5%, and 6.5% of patients following nonemergent noncoronary angiography, coronary angiography, and contrast-enhanced computed tomography, respectively [20]. In a study of 1111 hospitalized patients by Shema et al., CA-AKI, defined as an increase in serum creatinine of ≥0.5 mg/dl within 1–5 days, was identified in 44% of diabetic patients with underlying kidney disease [21]. D'Elia et al. demonstrated that 33% of patients with CKD developed CA-AKI, defined based on an increase in serum creatinine of ≥1.0 mg/dl following angiography [22]. Hence, the incidence is highly dependent upon the definition used, the characteristics of the patient population, and the nature of the procedure for which radiocontrast is administered.

Over the past decade, a series of studies have questioned the relationship between intravascular radiocontrast administration and CA-AKI, demonstrating comparable rates of AKI between patients who underwent radiographic procedures without contrast and patients who underwent contrast-enhanced procedures [23–31] (Table 11.1). Bruce et al. investigated the incidence of AKI, defined by an increase in serum creatinine ≥0.5 mg/dl or decrease in estimated glomerular filtration rate (eGFR) ≥25%, among 11 588 patients who underwent computed tomography either with ($n = 5790$) or without ($n = 7484$) intravenous (IV) contrast [23]. Among those with CKD, the incidence of AKI following computed tomography without contrast (8.8%) was comparable to the incidence following computed tomography with IV contrast (9.7% with iso-osmolal iodixanol and 9.9% with low-osmolal iohexol). Several subsequent studies demonstrated similar findings [26, 28, 32–34]. McDonald and colleagues conducted a meta-analysis comprising 13 studies with nearly 26 000 patients and reported a nonstatistically significant lower risk for AKI following IV contrast-enhanced procedures compared to unenhanced procedures (relative risk 0.79, 95% confidence interval [CI] 0.62–1.02) [35]. While the majority of such studies examined patients undergoing computed tomography, others have broadened the study population. In a study of hospitalized patients, Wilhelm-Leen et al. demonstrated a lower risk for AKI among hospitalized patients who received intravascular contrast as part of any type of procedure during their hospitalization compared with patients who did not receive contrast (5.1% vs. 5.6%, adjusted odds ratio [OR] 0.93, 95% CI 0.88–0.97) [26]. Caspi et al. demonstrated a similar incidence of AKI in a cohort of 2025 patients with ST segment elevation myocardial infarction treated with percutaneous intervention compared with 1025 patients treated with fibrinolysis (10.3% vs. 12.1%,

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Table 11.1 Studies comparing incidence of CA-AKI based on receipt of contrast.

Authors	Type of procedure	AKI with contrast (%)	AKI without contrast (%)	OR/RR (95% CI)
Bruce et al. [23]	CT	9.9/9.7[a]	8.8	Not reported
Ehrmann et al. [31]	Not specified	7.5	5.3	1.57 (0.69–3.53)
McDonald et al. [30]	CT	4.8	5.1	0.94 (0.83–1.07)
McDonald et al. [28][b]	CT	9.9	16	0.68 (0.55–0.84)
McDonald et al. [29]	CT	31	34	0.88 (0.75–1.05)
Hinson et al. [27]	CT	10.6	10.2	1.05 (0.94–1.18)
Caspi et al. [25]	Coronary angiography[c]	10.3	12.1	0.79 (0.60–1.05)
Zealley et al. [24]	Not specified	10.9	10.7	0.91 (0.82–1.00)
Wilhelm-Leen et al. [26]	Not specified	5.1	5.6	0.93 (0.88–0.97)

[a] Data denote AKI rates with iohexol and iodixanol, respectively.
[b] Comparison is for patients with stage 3 CKD.
[c] With percutaneous intervention.
AKI, acute kidney injury; CA-AKI, contrast-associated acute kidney injury; OR, odds ratio; RR, relative risk.

$P = 0.38$) [25]. In analyses that included propensity score matching, AKI rates remained comparable in patients who were and were not treated with percutaneous intervention (8.6% vs. 10.9%, $P = 0.12$).

While collectively these studies suggest that the administration of intravascular contrast does not increase the risk for AKI, most are retrospective in design and have limited capacity to adjust for the effects of unmeasured confounding. Specifically, patients at higher baseline risk for CA-AKI were likely to have selectively undergone radiological tests without intravascular contrast. Without understanding and accounting for the factors that might influence provider decision making regarding the use of contrast, the reported relationships are likely to be confounded by differences in baseline characteristics between those who did and those who did not receive contrast. This is best illustrated by the fact that certain of these studies demonstrated lower rates of AKI among patients who were administered intravascular contrast compared to those who did not receive contrast [26]. As contrast media are not nephroprotective, this observation strongly implies differential use of contrast based on clinicians' perceptions of patients' baseline risk for AKI. Accordingly, it is inappropriate to conclude based on these studies that the risk for AKI is independent of contrast administration in patients undergoing radiographic/angiographic procedures.

Risk Factors

Patient-related

Risk factors for CA-AKI are categorized as patient-related and procedure-related (Table 11.2). Patient-related conditions that augment the risk for CA-AKI are those that impair the capacity of the kidneys to effectively counteract the pathophysiological processes that lead to the development of CA-AKI. Pre-procedural kidney impairment is the most potent patient-related risk factor for CA-AKI, with lower levels of kidney function corresponding with higher degrees of risk [43]. In a study of 378 hospitalized patients undergoing nonrenal angiography, D'Elia et al. demonstrated a markedly higher incidence of CA-AKI among those defined as azotemic (blood urea nitrogen ≥30 mg/dl and serum creatinine ≥1.5 mg/dl) compared to nonazotemic patients (33% vs. 2%). Pre-existing azotemia was the only significant risk factor for CA-AKI in this study [22]. McCullough et al. documented a strong association of baseline kidney disease with risk of CA-AKI in a large population of patients undergoing angiography [38]. The findings from a trial by Rudnick et al. that compared different contrast agents suggest that diabetes, while not an independent risk factor for CA-AKI, substantially amplifies the risk in those patients with existing CKD [44]. Intravascular volume depletion, either absolute (e.g. GI losses) or effective (e.g. heart failure, liver failure), also increases the risk for CA-AKI [45, 46]. Similarly, the consumption of selective or nonselective nonsteroidal anti-inflammatory medications, which inhibit vasodilatory prostaglandins in the kidney, may also increase the risk for CA-AKI [47]. Other patient-related factors that have been linked with CA-AKI include increasing age, hypertension, anemia, and proteinuria; however, the independent associations of these factors with CA-AKI remain unproven as each is strongly linked with the presence and severity of CKD [48–51].

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Table 11.2 Association of CA-AKI with short-term mortality risk.

Study authors	*n*	CA-AKI definition	OR 95% CI
Clec'h et al. [36]	143	↑ Serum creatinine ≥25% or ≥0.3 mg/dl	3.48 (1.10–11.46)
Levy et al. [37]	357	↑ Serum creatinine ≥25% to ≥2.0 mg/dl	5.5 (2.9–13.2)
Shema et al. [21]	1 111	↑ Serum creatinine ≥50% or ↓ eGFR ≥25%	3.9 (1.2–12.0)
McCullough et al. [38]	1 826	↑ Serum creatinine >25%	6.6 (3.3–12.9)
From et al. [39]	3 236	↑ Serum creatinine ≥25% or ≥0.5 mg/dl	3.4 (2.6–4.4)
Rihal et al. [40]	7 586	↑ Serum creatinine >0.5 mg/dl	10.8 (6.9–17.0)
Bartholomew et al. [41]	20 479	↑ Serum creatinine ≥1.0 mg/dl	22 (16–31)
Weisbord et al. [42]	27 608	↑ Serum creatinine 0.25–0.5 mg/dl	1.8 (1.4–2.5)

CA-AKI, contrast-associated acute kidney injury; CI, confidence interval; eGFR, estimated glomerular filtration rate; OR, odds ratio.

Procedure-related

Factors associated with the radiological procedure itself also affect the risk for CA-AKI. The administration of larger volumes of radiocontrast increases the risk. Although the precise volume above which risk increases significantly not been definitively determined, various formulas to calculate the upper threshold dose in milliliters of contrast have been proposed. These include multiplying the body weight (in kg) by 5 and dividing by the patient's serum creatinine (mg/dl), or alternatively multiplying the patient's eGFR by 2 [52–55]. The performance of sequential radiocontrast procedures over a short period of time also increases the risk for CA-AKI. High-osmolal contrast media are associated with an increased risk compared with low- and iso-osmolal contrast [44, 56]. More widespread use of low and iso-osmolal contrast likely explains, at least in part, the trend toward lower overall rates of CA-AKI [57].

The intra-arterial administration of contrast appears to confer a higher risk compared with IV administration, although it remains unclear if the differential risk relates to the route of contrast administration or underlying characteristics that differ across patients undergoing different types of procedures. For example, Weisbord et al. demonstrated lower rates of CA-AKI following IV administration of contrast in the setting of computed tomography (6.5%) as compared with the intra-arterial administration for coronary (8.5%) and noncoronary angiography (13.2%) in patients with CKD [20]. However, differences in clinical characteristics such as diabetes mellitus, heart failure, or severity of CKD, along with differential utilization of preventive interventions such as IV fluids may have accounted for the differing incident rates across procedure types.

Associated Outcomes

Association with Short-term Adverse Outcomes

CA-AKI has been associated with an increased risk for short-term mortality (Table 11.2) [36–42]. McCullough et al. demonstrated that patients who developed CA-AKI following angiography with percutaneous coronary intervention were more likely to die during the index hospitalization compared to patients who did not develop CA-AKI (7.1% vs. 1.1%, I < 0.0001) [38]. Several other observational studies reported an increased incidence of short-term mortality risk associated with the development of CA-AKI [36, 37, 39–42] (Table 11.2). Data from clinical trials also document this association. In a clinical trial of acetylcysteine, Marenzi et al. reported a higher incidence of in-hospital death among patients who developed CA-AKI compared with patients without CA-AKI (26% vs. 1.4%, $P < 0.001$) [58]. Similarly, in a trial comparing IV fluids, Maioli et al. demonstrated that patients who experienced CA-AKI had a higher incidence of in-hospital death than patients who did not develop CA-AKI (11.1% vs. 0.2%, $P = 0.001$) [59]. CA-AKI has also been associated with increased duration of hospitalization, as noted in a study by Adolph et al., who found that the development of CA-AKI was associated with an average prolongation in hospitalization of 2 days [60].

Association with Longer-term Adverse Outcomes

Several studies demonstrate that CA-AKI is associated with increased longer-term risk of mortality and more rapid progression of underlying CKD [40, 59, 61–68] (Table 11.3).

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Table 11.3 Association of CA-AKI with longer-term risk of death.

Authors	*n*	CA-AKI definition	Follow-up (years)	Adjusted HR	95% CI
Goldenberg et al. [61]	78	↑ Serum creatinine ≥0.5 mg/dl or ≥25%	5	2.7	1.7–4.5
Solomon et al. [64]	294	↑ Serum creatinine ≥0.3 mg/dl	1	3.2[a]	1.1–8.7
Harjai et al. [62]	985	↑ Serum creatinine ≥0.5 mg/dl	2	2.6	1.5–4.4
Zlatanovic et al. [68]	1017	↑ Serum creatinine ≥0.5 mg/dl or ≥25%	4.8	2.6	1.3–3.8
Roghi et al. [63]	2860	↑ Serum creatinine ≥0.5 mg/dl	2	1.8	1.0–3.4
Rihal et al. [40]	7075	↑ Serum creatinine >0.5 mg/dl	0.5	[b]	[b]
Brown et al. [65]	7856	↑ Serum creatinine ≥0.5 mg/dl	7.5	3.1	2.4–4.0

[a] Denotes incident rate ratio of death, cerebrovascular accident, myocardial infarction, end-stage renal disease.
[b] Six-month mortality 9.8% vs. 2.3%, $p < 0.0001$.
CA-AKI, contrast-associated acute kidney injury; CI, confidence interval; HR, hazard ratio.

Solomon and colleagues reported that the development of CA-AKI was associated with a more than threefold increased risk of death, stroke, myocardial infarction, and/or end-stage kidney disease at 1 year following angiography [64]. Goldenberg et al. reported that patients with transient CA-AKI manifested a larger decrement in kidney function 2 years following angiography compared with patients who did not experience CA-AKI (ΔeGFR -20 ± 11 ml/min/1.73 m^2 vs. -6 ± 16 ml/min/1.73 m^2, $P = 0.02$), a finding consistent with other types of AKI [61]. James et al. demonstrated more rapid deterioration of kidney function over 3 months following angiography among patients who had developed CA-AKI compared to those without this condition (decrement in eGFR 0.8 ml/min/1.73 m^2/yr vs. 0.2 ml/min/1.73 m^2/yr) [66].

Potential Clinical Implications of Data Associating CA-AKI with Adverse Outcomes

While consistent in demonstrating associations of CA-AKI with serious, adverse short- and long-term outcomes, these and similar past studies have not established whether the associations are causal. CA-AKI, defined by small increments in serum creatinine, may simply be a marker of a population of patients with more significant vascular disease and propensity for hemodynamic instability that places them at heightened risk for serious events. This fact is particularly pertinent given research documenting the underutilization of clinically indicated, potentially life-saving contrast-enhanced procedures in patients with CKD [69–72]. This practice is referred to as "renalism" and is likely driven by providers' fear of precipitating CA-AKI.

Chertow et al. compared the use of invasive coronary care, including coronary angiography, percutaneous coronary intervention, and coronary artery bypass surgery, for the treatment of acute myocardial infarction in 15 093 patients with CKD and 42 191 without CKD [73]. In analyses accounting for the appropriateness of coronary angiography, those with CKD were around half as likely to undergo this procedure than patients without CKD (OR 0.47, 95% CI 0.40–0.52), and patients with CKD who did undergo coronary angiography were also less likely to proceed to revascularization (55% vs. 62%, $P < 0.0001$). Concern for the risk of CA-AKI was a hypothesized explanation for the underutilization of angiography and revascularization in subjects with CKD.

Renalism has also been documented among patients with CKD presenting with ST elevation myocardial infarction (STEMI). Nauta et al. found that rates of percutaneous coronary revascularization were lower in patients with STEMI and stage 4 CKD compared to those with STEMI but without CKD [72]. The findings of these studies documenting renalism are particularly relevant considering data from multiple studies demonstrating improved survival among patients with CKD who undergo coronary angiography and revascularization in the setting of acute coronary syndrome [74]. A study by Wright et al. of 1786 patients with CKD demonstrated that initial invasive coronary care was associated with 35% and 50% relative reductions in in-hospital mortality compared with conservative medical therapy in patients with ST elevation myocardial infarction and non-ST elevation myocardial infarction, respectively [75]. In a more recent study of patients with non-ST elevation acute coronary syndrome, James et al. found that among those with stage 3 CKD, early performance of coronary angiography was associated with lower long-term mortality (risk ratio 0.66, 95% CI 0.52–0.85) compared with conservative management, without a corresponding increase in risk for the development of end-stage kidney disease (risk ratio 0.88, 95% CI 0.42–1.86) [76].

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Collectively, these studies suggest that patients with CKD are less likely to undergo contrast-enhanced procedures than those without CKD and that this practice may be resulting in an increase in serious adverse outcomes. It is hypothesized that the underutilization of contrast-enhanced procedures in those with CKD is due to provider fear of causing CA-AKI. The importance of these observations is underscored by the absence of data establishing a causal link between CA-AKI and adverse downstream events. Efforts to examine whether CA-AKI causes adverse outcomes or simply serves as a marker of patients more likely to experience such events are essential. Until research answers this question, an important focus is ensuring that patients at risk for CA-AKI undergo indicated procedures, albeit with the implementation of evidence-based care to prevent this iatrogenic condition.

Prevention

Overview

CA-AKI is potentially preventable as the principal risk factors are well known and the timing of contrast administration is frequently known in advance, which facilitates the timely implementation of preventive care in patients most likely to benefit. Identifying patients at heightened risk for CA-AKI allows for the consideration of alternative imaging procedures that do not necessitate intravascular contrast, but that provide comparable diagnostic information. For at-risk patients who require procedures with intravascular contrast, evidence-based prevention should be implemented to reduce the risk for kidney damage.

Research on preventive strategies for CA-AKI has focused on comparing different contrast agents, using renal replacement therapy to filter iodinated contrast from the vasculature prior to glomerular filtration, administering pharmacologic agents to oppose the nephrotoxic actions of contrast, and expanding the intravascular space and enhancing urine volume with IV fluids to mitigate the adverse hemodynamic and tubular effects of contrast in the kidney.

Selection of Contrast Agent

Iodinated contrast media are commonly categorized based on their osmolality. First-generation contrast agents were ionic derivatives of tri-iodobenzoic acid with osmolalities of approximately 1500 to over 2000 mOsm/kg; accordingly, they were termed "high-osmolal" contrast media. Second-generation agents were nonionic monomers or ionic dimers with lower osmolalities (600–1000 mOsm/kg) and were referred to as "low-osmolal" contrast. Compared with high-osmolal contrast, the low-osmolal agents were associated with lower rates of CA-AKI. The Iohexol Cooperative Study was a clinical trial of 1196 patients undergoing coronary angiography that demonstrated a lower incidence of CA-AKI with low-osmolal iohexol compared with high-osmolal diatrizoate (3.2% vs. 7.1%, $P = 0.002$) [44]. A meta-analysis by Barrett and Carlisle that included results from this trial documented a lower risk of CA-AKI with low-osmolal contrast compared to high-osmolal contrast (OR 0.61, 95% CI 0.48–0.77) [56]. Among patients with impaired kidney function, low-osmolal contrast was associated with an even lower risk of CA-AKI compared with high-osmolal agents (OR 0.5, 95% CI 0.36–0.68).

The development of a third-generation contrast agent, iodixanol, a nonionic dimer that was iso-osmolal to plasma, led to comparisons with low-osmolal media. Initial trials suggested lower rates of CA-AKI with iodixanol compared with certain low-osmolal agents (i.e. iohexol, ioxaglate), while other studies demonstrated similar risk for CA-AKI [77–84]. Clinical practice guidelines from the American College of Cardiology/American Heart Association cite a lack of sound data to support the preferential use of iodixanol compared with low-osmolal contrast agents [85]. Similarly, the European Society of Urogenital Radiology supports use of iso- or low-osmolal contrast in patients at elevated risk of CA-AKI [86].

Renal Replacement Therapies

Iodinated contrast media remain largely in the extracellular space, have low protein binding, and are highly water soluble. Hence, they can be efficiently removed from the circulation by renal replacement therapies. Lee et al. randomized 82 patients with advanced CKD undergoing coronary angiography to receive prophylactic hemodialysis or not, in addition to IV saline and demonstrated a smaller decrement in creatinine clearance and lower likelihood of requiring chronic hemodialysis in those who received prophylactic dialysis [87]. Unlike this study, most other trials of prophylactic hemodialysis either failed to demonstrate a benefit or reported a higher risk for CA-AKI associated with prophylactic hemodialysis [88–93]. Continuous renal replacement therapy (CRRT) also removes iodinated contrast from the vascular space, and there have been two randomized clinical trials of continuous veno-venous hemofiltration that have suggested benefit [94, 95]. Both of these studies utilized change in serum creatinine relative to baseline as their primary outcome, an endpoint confounded by the lowering of serum creatinine by the intervention itself. As such, prophylactic renal replacement therapy as either intermittent hemodialysis or CRRT is not indicated to prevent CA-AKI.

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Pharmacological Agents

A multitude of clinical trials have investigated various pharmacological agents for the prevention of CA-AKI. Disappointingly, much of this literature has been susceptible to type 1 error and bias, and no prophylactic pharmacological treatments have been definitively demonstrated to be effective (Table 11.4).

By blocking active sodium transport in the ascending limb of the loop of Henle and reducing oxygen utilization, loop diuretics have been the subject of several studies. A clinical trial by Solomon et al. that compared IV hypotonic saline alone to IV hypotonic saline with either furosemide or mannitol reported a lower incidence of CA-AKI among patients who received peri-procedural IV hypotonic saline alone compared with IV hypotonic saline with furosemide (11% vs. 40%, $P = <0.02$) [96]. The lack of benefit with furosemide in this study mirrored the findings of an earlier study that found a higher risk for CA-AKI with the use of this agent [97]. A subsequent study by Majumdar et al. that attempted to ensure preservation of euvolemia despite diuretic administration again found increased risk of CA-AKI associated with administration of furosemide and mannitol [98].

On the basis of studies demonstrating renal vasodilatation when used in low doses, dopamine has been examined as a potential preventive therapy [99–101]. Initial studies suggested a beneficial effect on reducing CA-AKI, yet subsequent clinical trials with larger numbers of patients found no benefit [99, 101, 102]. Weisberg et al. compared dopamine with IV hypotonic saline with IV hypotonic saline and found no difference in the incidence of CA-AKI overall, yet reported that diabetics who received dopamine experienced higher rates of CA-AKI [101]. Fenoldopam is a selective dopamine receptor agonist that was found in early, mostly small nonrandomized studies, to prevent the development of CA-AKI [103–108]. As with dopamine, larger, methodologically stronger studies failed to demonstrate a benefit of fenoldopam [109].

A study by Kurnik et al. compared atrial natriuretic peptide (ANP), which has renal vasodilatory properties, with placebo in 247 patients with CKD and found no benefit for the prevention of CA-AKI in the ANP group [110]. Conversely, in a trial of 254 patients with CKD undergoing angiography, Morikawa et al. reported a lower incidence of CA-AKI among patients who received ANP and IV fluids compared to patients who received just IV fluids [111]. Notwithstanding the discordant findings on the benefit of ANP, this treatment has potentially deleterious side effects, such as reductions in systolic blood pressure, so its use for the prevention of CA-AKI is currently not recommended.

Adenosine has been implicated in the pathogenesis of CA-AKI. Accordingly, studies have evaluated antagonists of adenosine, including theophylline, for the prevention of this condition [112, 113]. In a trial by Early et al. that enrolled 80 patients, theophylline was not found to be effective for the prevention of CA-AKI [112]. Conversely, a study by Huber et al. of 100 patients with CKD undergoing coronary angiography demonstrated that pre-procedure theophylline was associated with a lower incidence of CA-AKI compared with placebo. Consistent with the findings of clinical trials, meta-analyses of theophylline have reported discordant findings [114–116]. Recognizing the potential adverse side effects of theophylline, particularly in patients with underlying cardiovascular disease, its use to prevent CA-AKI is not current recommended.

A multitude of clinical trials have investigated statins for the prevention of CA-AKI, many of which suggested a benefit, particularly with high intensity doses. The results of subsequent meta-analyses reflected the findings of the clinical trials upon which their results were based [117, 118]. However, a number of these studies enrolled lower risk patients and many used small increments in serum creatinine as the primary outcome, which may be problematic in light of the observation that the administration of

Table 11.4 Pharmacological interventions investigated for contrast-associated acute kidney injury prevention.

Ineffective	Effectiveness not determined
Mannitol[a]	Atrial natriuretic peptide
Loop diuretics[a]	Theophylline/aminophylline
Dopamine[a]	Statins
Fenoldopam[a]	Prostaglandin analogs
Calcium channel blockers	Allopurinol
N-Acetylcysteine	Acetazolamide
Sodium bicarbonate	

[a] Potentially deleterious.

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rosuvastatin may result in an increase in eGFR [119]. Consequently, there is insufficient evidence at present to conclude that statins are protective against CA-AKI.

N-acetylcysteine (NAC) is an antioxidant with vasodilatory effects that has been investigated in numerous trials over nearly 20 years as a preventive intervention for CA-AKI. The initial clinical trial of NAC by Tepel et al. randomized 83 patients undergoing computed tomography to receive oral NAC or placebo and demonstrated a lower incidence of CA-AKI with NAC (2% vs. 21%, $P = 0.01$) [120]. Since the publication of this study, dozens of clinical trials have examined NAC for the prevention of CA-AKI, but the literature has again been susceptible to type 1 error and variable study quality, yielding divergent results [58, 120–144]. Numerous meta-analyses sought to reconcile the incongruent findings of the clinical trials, yet similarly reported discordant results [116, 145–154]. The two largest studies, the Acetylcysteine for Contrast Nephropathy (ACT) trial and the Prevention of Serious Adverse Events Following Angiography (PRESERVE) trial, have provided more definitive evidence that NAC is not efficacious for the prevention of CA-AKI. The ACT trial randomized more than 2300 patients undergoing angiography to receive NAC or placebo and found no reduction in the risk for CA-AKI with NAC. Notwithstanding this finding, this study was limited by the inclusion of many patients at low risk for CA-AKI. Using a 2×2 factorial design, the PRESERVE trial randomized 2495 patients with CKD undergoing angiography to receive 1200 mg of oral NAC prior to and for 4 days following the procedure, and 2498 patients with CKD to receive matching oral placebo [155]. The results demonstrated no difference in the incidence of the primary trial endpoint comprised of 90-day death, need for dialysis, or persistent impairment in kidney function between patients randomized to receive NAC and those randomized to placebo (OR 1.02, 95% CI 0.78–1.33). Similarly, there was no difference in the incidence of CA-AKI, which was a secondary trial endpoint (OR 1.06, 95% CI 0.87–1.28). These two large trials provide sufficiently sound evidence that NAC has no role for the prevention of CA-AKI or associated serious, adverse outcomes.

Clinical trials of other agents including calcium channel blockers, prostaglandins, acetazolamide, and mannitol have been inconclusive, yet like the clinical trials of many pharmacological therapies were limited by small numbers of patients, reliance on a surrogate primary study endpoint defined by small increments in serum creatinine, and, in some cases, inclusion of patients at very low risk for kidney injury. Consequently, current recommendations for the prevention of CA-AKI do not incorporate the administration of any of these pharmacological therapies.

Intravenous Crystalloid

Administration of intravenous crystalloid is believed to reduce the risk of CA-AKI by counteracting contrast-induced vasoconstriction in the kidneys and by reducing the concentration and viscosity of contrast media in the tubular lumen [156]. Initial observational studies suggested a benefit of IV fluid, but were limited by the lack of randomization. A clinical trial by Trivedi et al. randomized patients undergoing coronary angiography to receive IV isotonic saline for 12 hours prior to and 12 hours following the procedure or unrestricted fluid by mouth [157]. The trial was stopped early after demonstrating a substantially lower incidence of CA-AKI among patients who received IV saline compared with oral fluid (3.7% vs. 34.6%, $P = 0.005$). Mueller et al. randomized over 1600 patients undergoing coronary angiography to receive peri-procedural IV 0.45% saline or 0.9% saline [158]. The administration of isotonic saline was associated with a lower incidence of CA-AKI than hypotonic saline (0.7% vs. 2.0%, $P = 0.04$), although the study population was at generally low risk for CA-AKI as evidence by the low event rates in both study arms.

Notwithstanding the limitations of these and other studies, IV isotonic saline was considered the standard treatment to prevent CA-AKI. It should be noted that a recent clinical trial questioned the need for IV fluid to prevent CA-AKI. The A MAstricht Contrast-Associated Nephropathy Guideline (AMACING) trial randomized 660 patients who were undergoing procedures with IV or intra-arterial contrast to receive IV isotonic saline or no IV fluids. Designed as a noninferiority trial, the investigators documented that a strategy of no IV fluids was not inferior to a strategy of IV saline for the prevention of CA-AKI (2.6% vs. 2.7%, absolute difference −0.10%, 95% CI −2.25 to 2.06) [159]. Despite this surprising result, key methodological issues, including under-enrollment (only 660 of 1300 planned patients were randomized), low rate of enrollment of patients undergoing procedures with intra-arterial contrast (48%) and interventional procedures (16%), and inclusion of a relatively large population of patients with less advanced CKD (i.e. eGFR 45–60 ml/min/1.73 m^2) substantially diminished the validity of the results.

Over the past 15 years, investigators have focused on comparing IV isotonic sodium bicarbonate with IV isotonic sodium chloride based on the hypothesis that enhanced urinary alkalinization with HCO_3^- decreases the generation of reactive oxygen species and may attenuate tubular epithelial cell injury compared with Cl^-. Merten et al. examined this hypothesis in a clinical trial that randomized 119 patients and documented that IV isotonic sodium

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bicarbonate was associated with a lower incidence of CA-AKI compared with IV isotonic saline (1.6% vs. 13.6%, $P = 0.02$) [160]. A proliferation of clinical trials followed with discordant results [59, 60, 161–168]. Multiple systematic reviews and meta-analyses reported results that were as disparate as the component clinical trials [162, 168–177]. More recently, Solomon et al. compared IV isotonic sodium bicarbonate to IV isotonic saline in 391 patients with eGFR <45 ml/min/1.73 m^2 undergoing angiography and found no differences in the incidence of a primary composite outcome of 6-month death, need for dialysis, or sustained 20% decrease in eGFR (14.9% vs. 16.3%, $P = 0.78$) [178]. This study also documented no difference in the incidence of CA-AKI between the study arms. The largest trial comparing the efficacy of sodium bicarbonate to saline was the PRESERVE trial, which randomized 4993 high risk patients to receive IV isotonic sodium bicarbonate ($n = 2511$) or IV isotonic sodium chloride ($n = 2482$) prior to, during, and following angiography [155]. Compared with IV saline, IV sodium bicarbonate use was not associated with a decreased risk for 90-day death, need for dialysis, or persistent impairment in kidney function (OR 0.93, 95% CI 0.72–1.22) or in the risk for CA-AKI (OR 1.16, 95% CI 0.96–1.41) [155]. A subsequent subgroup analysis of the PRESERVE trial found no benefit of IV sodium bicarbonate compared with IV sodium chloride among study participants who underwent percutaneous coronary intervention [179].

A series of small studies examined the efficacy of inducing a very high urine flow (>300 ml/h) with saline and furosemide using a device that permits accurate matching of urine flow and IV saline administration for the prevention of CA-AKI. A recent meta-analysis by Shah et al. that comprised three clinical trials and 586 patients demonstrated a reduction in CA-AKI, major adverse clinical events, and need for renal replacement therapy with this device compared with standard preventive care comprised principally of conventional isotonic IV fluid administration [180]. However, as pointed out by the authors, these findings were based on small, underpowered studies and require confirmation in larger, adequately powered clinical trials.

While heart failure is recognized as a risk factor for CA-AKI, there are data that the administration of IV fluids to patients with heart failure is both effective and safe. The Prevention of Contrast Renal Injury with Different Hydration Strategies (POSEIDON) trial randomized 396 patients who were undergoing coronary angiography and compared a standard regimen of IV isotonic saline (3 ml/kg for 1 hour prior to and 1.5 ml/kg/h during and for 4 hours following the procedure) with a strategy of IV isotonic saline based on the left ventricular end-diastolic pressure value at the beginning of angiography [181]. As compared to the standard treatment group, who received IV isotonic saline at 1.5 ml/kg/h during and for 4 hours after the procedure, the experimental group received IV isotonic saline based on the measured left ventricular end-diastolic pressure (i.e. 5, 3, or 1.5 ml/kg/h for left ventricular end-diastolic pressure measurements of <13, 13–18, and >18 mmHg, respectively). CA-AKI occurred less commonly in the left ventricular end-diastolic pressure-guided group (6.7% vs. 16.3%, relative risk 0.41, 95% CI 0.22–0.79, $P = 0.005$) compared with the standard IV saline group. The overall rate of pulmonary compromise related to IV fluid administration was very low [181]. A similar study by Qian et al. demonstrated a lower incidence of CA-AKI in patients who received IV saline administered based on central venous pressure measurements compared with patients who received standard IV saline treatment [182]. The overall rate of acute heart failure during IV fluid administration was very low and comparable across patient groups (3.8% vs. 3.0%, $P = 0.5$).

Limitations of Clinical Trials on Preventive Interventions

Many of the clinical trials investigating preventive interventions for CA-AKI had important methodological limitations. Most importantly, the vast majority of trials used small increments in serum creatinine as their primary outcome, based on observational data associating such biochemical perturbations with serious, adverse events. That such correlations exist is not in dispute, but it is essential to recognize that for these serum creatinine changes to truly be considered a "surrogate" for serious adverse clinical events, they "must track with the frequency of the end point (i.e. serious clinical events) both as an epidemiologic marker and as a therapeutic responder" [183]. Definitive evidence that the changes in serum creatinine that define CA-AKI track with changes in subsequent clinical outcomes is lacking. Thus, although CA-AKI remains defined by small changes in serum creatinine, definitive clinical trials require the use of more meaningful outcomes.

The use of small changes in serum creatinine as the surrogate primary endpoint has resulted in multiple clinical trials that are susceptible to type 1 error with inflated event rates, small sample sizes, and inadequate statistical power to discern effects of the interventions on key patient-centered outcomes. Clinical trials focused upon far more serious patient-centered outcomes (e.g. death, need for dialysis) as the primary study outcome require markedly larger samples sizes, as was demonstrated with the PRESERVE trial [155]. As such, all trials of treatments to prevent CA-AKI need to use clinically significant events as

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their primary outcome until there is sound evidence that prevention of small changes in serum creatinine also diminishes these "hard" outcomes.

Current Recommendations for Prevention

Identifying patients at high risk for CA-AKI and determining if alternative imaging procedures that can avoid intravascular iodinated contrast with comparable diagnostic yield are available should be the initial step in efforts to prevent this condition. For most patients who require procedures with the use of intravascular contrast, all modifiable risk factors should be addressed. Nephrotoxic medications such as nonsteroidal anti-inflammatory medications should be discontinued prior to contrast administration and held until CA-AKI has been ruled out. The lowest required dose of either low or iso-osmolal contrast should be used. Isotonic IV sodium chloride should be administered prior to, during, and after the procedure, particularly for patients with lower eGFR values and those undergoing angiography [155]. While IV isotonic sodium bicarbonate is an acceptable alternative, it offers no advantage over IV isotonic saline and poses a small risk for compounding errors as there is currently no commercially available "off-the-shelf" form. For hospitalized patients, isotonic IV saline can be administered at a rate of 1 ml/kg/h for 12 hours preceding, during, and for 12 hours following the procedure if the timing of the procedure permits. An alternative regimen, particularly for outpatients and those undergoing more urgent procedures, includes IV isotonic saline at a rate of 3 ml/kg/h over 1–2 hours prior to and 6 ml/kg infused over 2–6 hours following contrast administration. IV isotonic saline should be administered to patients with nondecompensated heart failure with careful monitoring of patients' respiratory status. There is no current role for the use of pharmacological agents for the prevention of CA-AKI. Similarly, studies to date do not support the discontinuation of diuretics or blockers of the renin-angiotensin aldosterone axis prior to contrast administration. While a meta-analysis by Wu et al. that comprised 14 studies demonstrated a higher risk for CA-AKI among patients receiving angiotensin converting enzyme inhibitors or angiotensin receptor blockers at the time of angiography compared with patients not receiving these medications, that authors acknowledged this finding was based on low-level evidence from small observational studies [184]. Furthermore, the initiation or discontinuation of these agents at the time of contrast administration may confound the interpretation of small changes in serum creatinine. Assessing for the development of CA-AKI by monitoring serum creatinine 48–96 hours following contrast administration is important to identify the development of this condition and to provide supportive care to attenuate the risk for further renal parenchymal damage.

Conclusion

AKI remains a common iatrogenic event following procedures that involve the intravascular administration of iodinated contrast. The pathophysiology of and risk factors for CA-AKI have been demonstrated in past studies, as have the associations of this condition with serious, adverse short- and long-term outcomes. Such associations, which have not been confirmed to be causal, have likely led to the underutilization of clinically indicated diagnostic and therapeutic contrast-enhanced procedures in patients with CKD. Patients with clear clinical indications for procedures that require intravascular contrast should undergo such procedures, albeit with the implementation of evidence-based preventive care. The cornerstone of prevention presently is the peri-procedural IV administration of isotonic crystalloid, preferably sodium chloride. Well-designed, adequately powered studies that utilize clinically relevant primary outcomes and that enroll high-risk patients are needed to expand our understanding of the clinical implications and prevention of this iatrogenic condition.

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12

Miscellaneous Etiologies of Acute Kidney Injury

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Introduction

This chapter will review some of the less frequent causes of acute kidney injury (AKI): acute interstitial nephritis (AIN), atheroembolic renal disease, cast nephropathy, crystalline nephropathies, and renovascular syndromes. Due to the relative rarity of these conditions, there are few randomized controlled trials to guide management. However, several observational and retrospective studies provide some insight into the clinical features, natural histories, and therapeutic responses.

Acute Interstitial Nephritis

Definition, Etiology, and Pathogenesis

AIN is a hypersensitivity reaction that causes AKI by immune-mediated tubular injury localized to the kidney interstitium with sparing of the glomeruli. The first description of AIN was by Biermer in 1860 [1]. In 1898, Councilman used the term acute interstitial lesions to describe the histopathological changes noted in autopsy specimens of children who had succumbed to scarlet fever, diphtheria, and other infectious diseases [2]. In 1946, sulfonamides became one of the first drugs noted to cause intestinal nephritis [3] followed by penicillin and methicillin in 1968 [4]. The true incidence of AIN is difficult to ascertain but data from various literature searches provide estimates of 0.5–3% of all kidney biopsies and 5–27% of biopsies done for AKI [5–7]. The etiology of AIN is estimated to be drug-induced in as many as 78% of cases in developed countries while infectious etiologies are noted in 50% of cases from developing countries.

AIN is a delayed hypersensitivity reaction mediated by T-cells, which may occur through diverse mechanisms, including molecular mimicry with tubular epitopes or deposition of immunogenic portions of the inciting agent in the kidney interstitium, either alone or as a hapten [8]. This is usually not dose-dependent, but idiosyncratic with recrudescence in disease activity upon re-exposure to compounds with similar biochemical structure, often with multiorgan involvement. Newer chemotherapeutic agents, including immune checkpoint regulators and programmed cell death proteins, cause dose-dependent toxicity by immune upregulation [9]. On histology, there are focal to diffuse interstitial infiltrates composed of T-cell predominant lymphocytes. Immune complexes or antitubular basement membrane antibodies are infrequently noted, suggesting that humoral immunity may also be involved [10, 11]. Granulomatous interstitial nephritis (GIN) has been identified in approximately 0.5–0.9% of all kidney biopsy specimens. Approximately 17.5–45% of GIN is attributed to drug toxicity [12]. The most common etiologies of AIN are drugs (70%), autoimmune diseases (20%), infections (4%), and idiopathic (5%) [5] (Table 12.1). Antibiotics (49%), proton pump inhibitors (14%), and nonsteroidal anti-inflammatory drugs (NSAIDs; 11%) accounted for the majority of cases, although any drug can potentially cause AIN [5]. The offending drug may be difficult to identify due to polypharmacy [13].

Clinical Features

The classical signs and symptoms of drug-induced AIN include a triad of rash, fever, and eosinophilia [14], which suggests an allergic type reaction. However, it should be noted that the constellation of the three findings is an exception and not the rule. These allergic symptoms may be absent, especially in those cases associated with NSAID, where nonspecific symptoms of acute kidney failure including nausea, vomiting, malaise, and fatigue maybe seen. Oliguric or nonoliguric kidney dysfunction can occur. The latent period for disease manifestation is

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Table 12.1 Etiology of acute interstitial nephritis.

Drugs	Antibiotics	Penicillin[a] (penicillin, ampicillin, and methicillin), cephalosporins, fluoroquinolones[a] (ciprofloxacin, levofloxacin), rifampin[a] and sulfonamides[a] (including cotrimoxazole) Abacavir, acyclovir, indinavir
	NSAIDs	Celecoxib, diclofenac, fenoprofen, indomethacin, meloxicam, sulindac Mesalamine, sulfasalazine
	Antacid/antisecretory	Esomeprazole, omeprazole, pantoprazole Cimetidine, ranitidine, famotidine
	Chemotherapeutic agents	Atezolizumab, iplilimumab, nivolumab, pembrolizumab Sorafenib, sunitinib Adriamycin, BCG, bevacizumab, bortezomib, gemcitabine, lenalidomide, pemetrexed
	Diuretics	Chlorthalidone, hydrochlorothiazide, metolazone, furosemide, amiloride, triamterene
	Antihypertensive	Captopril, lisinopril, losartan, amlodipine, nifedipine
	Anticonvulsants	Carbamazepine, levetiracetam, phenobarbital, phenytoin, valproic acid
	Miscellaneous	Allopurinol, atorvastatin, carbimazole, feboxustat, gemfibrozil, leflunomide, sildenafil
Infectious agents	Bacteria	*Brucella* spp.,[a] *Campylobacter jejuni*, *Corynebacterium diphtheriae*, *Chlamydia* spp., *Escherichia coli*, *Legionella* spp., *L. interrogans*, *Mycobacterium tuberculosis*,[a] *Mycoplasma pneumoniae*, *Rickettsia* spp., *Salmonella* spp.,[a] *Staphylococcus* spp., *Streptococcus* spp., *Yersinia pseudotuberculosis*
	Virus	Cytomegalovirus, Epstein–Barr virus,[a] hantaviruses, hepatitis B virus, human immune deficiency virus, herpes simplex virus, measles virus, polyomaviruses
	Parasites	*Leishmania donovani*, *Toxoplasma gondii*[a]
Systemic diseases		Sarcoidosis,[a] Sjogren's syndrome,[a] systemic lupus erythematosus, tubulointerstitial nephritis and uveitis syndrome,[a] Antineutrophil cytoplasmic antibody-associated vasculitis, other vasculitis

[a] Denotes association with granulomatous interstitial nephritis.

usually 3 weeks after the initiation of the offending drug in 80% of individuals, with an average of 10 days (although can range from 1 day to more than a year). NSAIDs have a slightly longer latency of 2–3 months. The temporal relationship between the initiation of a new drug and the development of kidney injury may also aid in making the diagnosis. Disease manifestations develop within 3 weeks of initiation of the offending drug in about 80% of patients, with an average latency of onset of 10 days (range 1 day to >1 year) [8]. The duration of onset may be longer when associated with NSAIDs, with a mean latent period of 2–3 months [15]. When AIN is associated with a systemic disease, the clinical features of the respective diseases may be present (Table 12.2).

Laboratory Diagnosis

Urinalysis in patients suspected to have AIN often show hematuria and/or sterile pyuria, but these are nonspecific findings. The presence of white blood cell (WBC) casts is more specific, although they can also be seen in pyelonephritis and certain proliferative glomerulonephritis. Eosinophiluria (urine eosinophils >1% of the urine WBCs) can be seen, usually detected more reliably with Hansel's stain than with Wright's stain [23]. However, the diagnostic utility of testing for urine eosinophils has recently been invalidated and is no longer recommended. In a retrospective study of 566 patients who had urine eosinophil testing and a kidney biopsy within a week of each other, 91 patients had evidence of AIN on pathology. Urine eosinophils at 1% and 5% cutoff had sensitivities of 30.8% and 19.8% and specificities of 68.2% and 91.2%, respectively [24]. Urine chemistries are not useful in distinguishing AIN from other etiologies of AKI. Fractional excretion of sodium can either be above or below 1% [25].

Other laboratory abnormalities that may be present include metabolic acidosis secondary to renal tubular acidosis, low specific gravity due to a concentrating defect, glycosuria, or phosphaturia secondary to Fanconi syndrome. Mild proteinuria is common, but sometimes it may be in the nephrotic range. Though heavy proteinuria has been reported with AIN from various drugs, it is classically associated with NSAIDs. Concomitant minimal change glomerulopathy may be seen in NSAID-associated AIN, although the exact incidence is unclear. One paper noted that 70% of patients with NSAID-associated AIN had

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Table 12.2 Causes of AIN and characteristic clinical and laboratory features.

Inciting agent [reference(s)]	Clinical features	Laboratory findings	Clinical course
All drugs other than methicillin [2, 8, 9]	Fever (45%) Rash (42%) Arthralgia (12%) Flank pain (45%) Oliguria (40%) Macroscopic hematuria (17%) New or worsened hypertension (20%)	Hematuria (53%) Pyuria (50%) Mild proteinuria (58%) Eosinophilia (40%)	Mean 10-day exposure prior to onset Temporary dialysis required in 32–50% CKD remains in 36–40%
Methicillin [2, 8]	**Hypersensitivity symptoms common:** **Fever** (85%) Rash (25%) Arthralgias (10%) • Oliguria (25%) **Macroscopic hematuria** (80%)	Hematuria (90%) Pyuria (95%, often w/WBC casts) Mild proteinuria (80%) **Eosinophilia** (80%) **Eosinophiluria** (almost all patients)	Mean duration of impaired kidney function, 1.5 months Temporary dialysis required in 17% **CKD remains in only 10%**
NSAIDs [2, 8–10]	**Hypersensitivity symptoms uncommon**: Fever, rash, or arthralgias (10%) Macroscopic hematuria (7%) New or worsened hypertension (17%)	**Nephrotic-range proteinuria** (38%) Hematuria (38%) Pyuria (40%) Eosinophilia (40%) Kidney biopsy may also show **minimal change disease**	**Mean exposure 2–3 months before presentation** Temporary dialysis required in 20–38% **CKD remains in 56%**
Allopurinol [10]	**Hypersensitivity symptoms very common and robust** Signs of vasculitis possible **Often occurs in setting of renal insufficiency** from accumulation of the inciting metabolite, oxypurinol	**Eosinophilia** fairly common **Hepatitis** common Kidney biopsy may reveal **immune complex deposition at TBM**	**Mortality may be as high as 25%** Rate of kidney recovery unknown
Rifampin [16]	**Hypersensitivity symptoms common and robust** Fever (45%) **Nausea or vomiting** (72%) **Abdominal pain** (40%) Rash uncommon Flank pain (17%) **Oligo-anuria** (96%)	Eosinophilia (7%) Coombs-positive **hemolysis** (25%) **Thrombocytopenia** (50%) **Hemoglobinuria** (17%) Hepatitis (25%) **Antirifampin antibodies** (almost all patients) Kidney biopsy rarely shows immune complex deposition at TBM	**Usually occurs 24 hours after dose** with current intermittent dosing or after previous continuous exposure (up to 1 year prior) Dialysis required in almost all cases **CKD remains in only 3%**

(*Continued*)

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Table 12.2 (Continued)

Inciting agent [reference(s)]	Clinical features	Laboratory findings	Clinical course
PPI [17]	Fever (<50%) Rash (<10%) Eosinophilia (33%) Fatigue and nausea (39%) Weakness (22%)	Pyuria Hematuria White and red cell cast Biopsy: interstitial infiltrates with or without tubulitis	Median time from exposure to diagnosis exceeds 6 months Absolute risk for CKD is increased (3.3%)
Checkpoint inhibitors [9]	Systemic manifestations (pneumonitis, vasculitis, colitis, hepatitis, pancreatitis, myocarditis, enteritis, neuropathy) occur with varying frequency	Eosinophilia Kidney biopsy may show AIN and/or glomerulonephritis and membranous GN	Usually occur 3–12 months after starting treatment. Treatment of choice is prednisone and stopping CPI CPI is restarted after improvement in SCr
Leptospirosis [18]	Preceding **exposure to animal excrement** Fever (93%) **Jaundice** (93%) Hepatomegaly (76%) Gingival/GI **bleeding**, purpura (79%) Macroscopic hematuria (26%) **Conjunctival suffusion** (12%) Altered mental status (50%) Hypotension (62%) **Oligoanuria** (95%) Rhabdomyolysis (62%)	**Cholestatic hepatitis** (93%) **Hemolytic anemia** (72%) **Thrombocytopenia** (81%) **Hypokalemia** (renal wasting) (38%) **Hyponatremia** (79%) Rhabdomyolysis (62%) **Positive blood/urine cultures or serology** Kidney biopsy reveals inflammation predominating at proximal tubules early; interstitial hemorrhage possible	Nephropathy occurs in 40% of cases of leptospirosis **Mortality of 26%** Temporary dialysis required in 74% **Persistent tubular transport defects may remain in 29%** CKD remains in only 10.3%
BK nephropathy [14]	Usually occurs in kidney allografts 1 year after transplant in setting of **aggressive immunosuppression** May occur in other immunosuppressed states also (e.g. HIV) Fever uncommon Macroscopic hematuria rare	**Decoy cells** (tubular cells with enlarged nucleus, intranuclear inclusions) in urine sediment, 100% sensitivity/71% specificity **Viremia by PCR** 100% sensitive/88% specific Kidney biopsy reveals **SV40 stain positive intranuclear inclusion bodies**	Acute or gradual deterioration in kidney function Decreases 5-year kidney allograft survival from 76% to 46% Often **resolves with decrease in immunosuppression**

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Sarcoidosis [19]	Extrarenal symptoms of sarcoidosis predominate with **pulmonary, ocular, and skin symptoms** most common Renal limited disease is very rare Most often occurs in young adults Higher incidence in black population	Eosinophilia (25%) **Hypercalcemia** or normocalcemia despite advanced kidney failure **Chest radiography with hilar adenopathy** and/or infiltrates (90%) Elevated ACE level not reliable with kidney involvement Renal biopsy reveals **noncaseating granulomas** and giant cells	Often a remitting/relapsing course responsive to pulse increase in steroids **CKD remains in 90%**
TINU [20]	3 : 1 female predominance **Median age of onset, 15 years** **Eye pain or redness** (32%) Fever (53%) Weight loss (47%) Abdominal or flank pain (28%) Arthralgias or myalgias (17%) Rash (1%)	Eosinophilia (17%) **Elevated serum IgG** (83%) Kidney biopsy shows granulomas in 13%; unlike sarcoidosis, uveitis is not granulomatous	Uveitis precedes renal disease in 21%, is concurrent in 15%, and follows it in 65% **Complete renal recovery often occurs spontaneously within 1 year** Uveitis recurs in 54%, but recurrence of AIN is rare CKD is rare
IgG4 disease [21]	Pancreatitis Sclerosing cholangitis Autoimmune hypophysitis Sialadenitis Interstitial lung disease Retro-peritoneal and mediastinal fibrosis	**Elevated IgG4** levels Biopsy shows lymphoplasmocytic infiltrates of IgG4-plasma cells, storiform fibrosis, tissue eosinophilia and obliterative phlebitis	Good response to corticosteroids but recurrence is common.
DRESS syndrome [22]	Fever Lymphadenopathy Rash that can progress to Exfoliative dermatitis **Hepatitis** Pneumonitis Myocarditis Nephritis Colitis	Leukocytosis with **eosinophilia** (90%) or **mononucleosis** (40%) Anemia Thrombocytopenia Elevated liver enzymes	High mortality rates up to 10% from fulminant hepatitis Supportive treatment including glucocorticoids

CKD, chronic kidney disease; CPI, checkpoint inhibitor; DRESS, drug reaction with eosinophilia and systemic symptoms; GI, gastrointestinal; IgG, immunoglobulin G; PPI, proton pump inhibitors; SCr, serum creatinine; SV40, simian virus 40; TBM, tubular basement membrane.
Particularly distinctive features are noted in bold. The percentages are estimates of the prevalence of the associated finding for each etiology.

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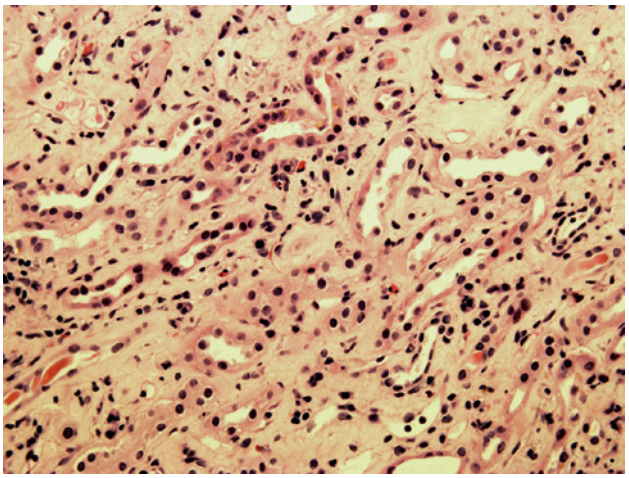
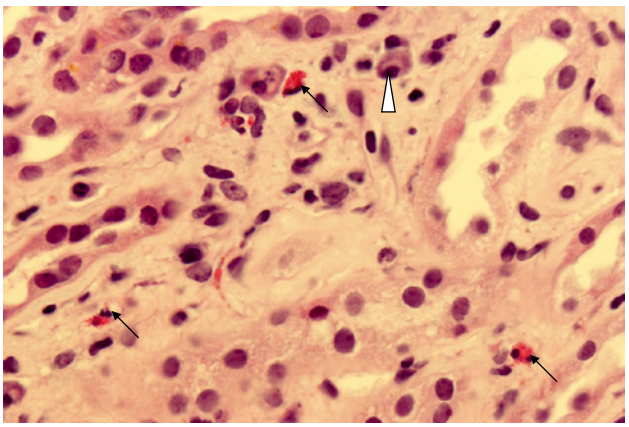
nephrotic range proteinuria [8]. Signs of multiorgan dysfunction, such as elevated transaminases and hemolysis, are occasionally seen.

Kidney imaging may reveal normal to large kidneys with increased echogenicity, although this is a nonspecific finding [25]. Gallium scintigraphy and 2-[18F]-fluor o-2-deoxy-D-glucose-positron emission tomography (FDG-PET) scanning have shown some promise in diagnosis of AIN, but lacks sufficient sensitivity and specificity to be recommended as diagnostic tools. Kidney biopsy is the gold standard for the definitive diagnosis of AIN. A cellular infiltrate consisting mostly of T-cells and macrophages with edema increases the separation of tubules from one another, and there may be tubulitis or frank tubular necrosis in severe AIN (Figure 12.1a,b). Neutrophils, eosinophils, and plasma cells can often also be found in the cellular infiltrate. The presence of neutrophils may be associated with better response to steroid therapy [26]. Occasionally there is granulomatous inflammation, which might provide clues as to the offending agent, since this is associated with a limited list of causes (Table 12.1). Immunofluorescence and electron microscopy usually do not reveal the presence of immune complexes, but tubular basement membrane deposition can rarely be seen. Glomeruli are usually normal, but electron microscopy may reveal foot process effacement in NSAID-associated AIN. A summary of the relevant laboratory findings is given in Table 12.2.



(a)



(b)

Figure 12.1 Acute interstitial nephritis (AIN), drug-induced, with hematoxylin and eosin stain. Note the presence of interstitial edema and predominantly mononuclear inflammatory cells separating the normally adjacent tubules (a). A few eosinophils (arrows) and a plasma cell (arrowhead) can be seen on higher power (b). *Source:* Courtesy of Rosa Davila MD, Washington University School of Medicine.

Course and Treatment

Given the polymorphic nature of the disease and the multiple potential causative agents, AIN does not have a uniform course or response to treatment. In the prototype, methicillin-induced AIN, the prognosis was excellent, with complete recovery of kidney function noted in 90% of patients after a mean period of 1.5 months after cessation of the drug exposure [2]. In nonmethicillin, drug-induced AIN, chronic kidney disease (CKD) is an expected sequela in 36–40% of cases [2]. The prevalence of CKD is even higher (56%) with NSAID-induced AIN [27]. In one series consisting of seven cases of infection-associated AIN, all had complete renal recovery. However, in this case series the inciting infections were readily treatable or self-limited [13, 27]. Indeed, the prognosis for AIN may depend on the promptness of elimination of the inciting agent, with those etiologies associated with milder symptoms and therefore delayed diagnosis (e.g. NSAIDs, chronic infections, sarcoidosis) having worse prognosis than those with more acute and dramatic presentations (e.g. methicillin, rifampin, acute bacterial, or viral infections) (Table 12.2).

Due to the heterogeneity of AIN and severity of the illness, most studies that guide therapy in AIN are retrospective and there is a dearth of randomized controlled trials to define therapeutic strategies. Clearly, the most important therapeutic maneuver is prompt removal of the inciting agent. Corticosteroids have been used in the treatment of hypersensitivity, although the benefits of its use remain controversial. Clarkson et al. studied 60 patients with AIN (92% drug-induced), 60% of whom were treated with corticosteroids, and found no difference in serum creatinine at 1 year between those who received and did not receive corticosteroids [28]. In contrast, Gonzales et al. reported that use of steroids was beneficial, especially when started early, being associated with a lower final serum creatinine

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and less need for renal replacement therapy (RRT) [29]. In a single center, retrospective analysis from 1993 to 2011 which studied 133 patients with biopsy proven AIN (70% drug-induced AIN), 49% of patients with drug-induced AIN achieved complete recovery after initiation of corticosteroids. An additional 39% of patients had partial recovery and 12% had no recovery. Correlates for poor recovery included longer duration of exposure to the drug and time to initiation of steroids [5]. A more recent, large, single-center retrospective study from London included 187 eligible patients with AIN out of 3983 native kidney biopsies, and 158 patients were treated with steroids. It was concluded that steroid-treated patients had higher eGFR at all follow-up intervals up to 24 months. Fewer patients were dependent on RRT at the end of 6 months and 24 months (3.2% and 5.1%) when compared to patients not treated with steroids (20.6% and 24.1%, respectively) [30]. An attempt to match steroid-treated with untreated patients showed greater improvement in renal outcomes, although this was not statistically significant. Based on their results, the authors suggested a regimen of prednisolone at 1 mg/kg with a maximum dose of 60 mg daily, with rapid weaning over 8–12 weeks to prevent worsening of kidney function. However, one must be careful in extrapolating this data to all patients with AIN, since this study only looked at patients with biopsy proven AIN and may not have included those who had improvement in renal function after prompt withdrawal of the offending agent at the onset of kidney injury.

One retrospective series described the use of mycophenolate mofetil in eight cases of steroid-dependent AIN, defined as worsening kidney function with steroid withdrawal, even after a 6-month course of corticosteroids. Only two of the eight cases were thought to be drug-induced, with the remaining cases being idiopathic or associated with systemic diseases such as sarcoidosis or collagen vascular disease. Treatment with mycophenolate mofetil resulted in a stabilization or slight improvement in kidney function (mean creatinine decreased from 2.3 to 1.6 mg/dl); however, an average of 2 years of therapy was required [31]. More recently a case report demonstrated benefit of antithymocyte globulin in a patient on RRT as the result of steroid refractory AIN who achieved independence from hemodialysis following treatment [32].

Given these data, a reasonable treatment strategy would be to reserve corticosteroids for patients with idiopathic AIN, systemic diseases for which corticosteroids have a proven role (e.g. sarcoidosis, Sjögren's syndrome, vasculitides), or cases with characteristics associated with worse renal prognosis. The latter includes delayed onset of kidney recovery after removal of the inciting agent (>1 week), prolonged exposure to the offending agent (>2–3 weeks), preexisting CKD, and histology with intense and diffuse interstitial infiltrate, granuloma formation, or significant fibrosis and tubular atrophy. If corticosteroids are considered, then they should be given early, as this is associated with improvement in kidney function [33]. A frequently used regimen is oral prednisone, 1 mg/kg, with the duration of therapy guided by the improvement in kidney function, usually 3 weeks. The presence of conditions that can be exacerbated by corticosteroid therapy (e.g. slow-healing wounds, brittle diabetes, or active infection) should dissuade the clinician from this option. Furthermore, studies have suggested that corticosteroids do not alter the course of NSAID-induced AIN [28], but if poor prognostic factors are present, treatment can still be considered. Other immunosuppressants should be reserved for cases that are not responsive to withdrawal of the inciting agent alone when corticosteroid resistance or dependence occurs.

Atheroembolic Renal Disease

Definition, Prevalence, and Pathogenesis

Atheroembolic renal disease causes progressive AKI and acute kidney disease (AKD) resulting from inflammation in the renal microvasculature caused by cholesterol crystals and lipid debris. The dislodged atheromatous plaques can travel through the bloodstream and affect any organ, including the kidneys, skin, brain, and gastrointestinal system. Atheroembolism often occurs after an inciting event (like cardiac catheterization, vascular surgeries, etc.) or use of systemic anticoagulation but may occur spontaneously. The first description of atheroembolic disease was by Panum in 1883, but the nature of cholesterol embolization was described by Flory in 1945 [34].

The disease is often under recognized. From various autopsy studies, the incidence was about 1% but increased to 4.0–6.5% in people 60 years or older [35]. There is usually an inciting event leading to plaque destabilization and distal showering of lipid debris. Plaque destabilization may occur from vessel wall trauma from vascular surgery or endovascular procedures of which coronary angiography is the most common iatrogenic procedure causing atheroembolism. Although less common as an inciting factor, systemic anticoagulation and thrombolytics are thought to prevent protective thrombus formation over ulcerated plaques, thereby increasing risk of atheroembolism.

In atheroembolism, the cholesterol-containing debris lodge in small arterioles, inciting thrombus formation, and causing distal ischemia and infarction. Within 5 days there may be recanalization of the thrombus, but an inflammatory foreign body arteritis ensues. Because the cholesterol is not soluble and it is never successfully cleared by phagocytes, inflammation persists and leads to progressive

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fibrosis and later obliteration of the lumen of the small vessel. With involvement of multiple arterioles, the result is persistent, patchy ischemia of several nephrons, instigating progressive renal insufficiency.

Clinical Features and Laboratory Findings

Atheroembolic renal disease is preeminently a disease of the elderly (mean age 66–70 years), with a male predominance (4 : 1). It has a higher incidence in whites than African Americans (30 : 1) [36]. It is possible that this discrepancy represents under-recognition of the disease in the African American population, as the characteristic skin changes may by missed in dark-skinned individuals. The major risk factors include age more than 60 years, male gender, comorbidities like diabetes mellitus and hypertension, and tobacco use. Also, patients with significant aortic atherosclerosis have a higher incidence of cholesterol embolic disease [34]. The onset of disease is quite variable, ranging from 3 days to 3 months (as the embolic shower is often unpredictable). As mentioned earlier, in addition to the kidneys, any organ system may be involved, including skin, gastrointestinal, and brain. Transient eosinophilia (seen in 48%) and elevated erythrocyte sedimentation rate and occasionally hypocomplementemia may be present [37]. The characteristic skin changes include livedo reticularis or "blue toe" syndrome. These constellations of clinical and laboratory features often mimic a systemic vasculitis (Table 12.3).

Renal histology reveals empty clefts in arcuate and interlobular arteries and, less commonly, afferent arterioles. These result from the dissolution of lipid from these sites by the fixation process leaving voids at the sites of cholesterol crystals. Depending on the age of the lesion, varying degrees of arteritis and intimal fibrosis can be seen (Figure 12.2). In severe, acute cases there may be signs of acute tubular necrosis (ATN). Late in evolution, patchy glomerular sclerosis and tubular atrophy may be visualized in areas supplied by the affected vessels. Similar arteriolar inflammation or fibrosis can be found in other tissues, especially the muscle, gastrointestinal tract, and skin. Biopsy of skin lesions may have the highest diagnostic yield, with a reported sensitivity of 92% [43].

Table 12.3 Clinical findings in patients with renal atheroembolic disease and frequency of occurrence.

Clinical finding	Frequency of occurrence (%)
Signs and symptoms	
New-onset, accelerated, or labile hypertension	78
Skin findings (cyanotic or ulcerated digits or scrotum, livedo reticularis on back or lower extremities, nodules, less commonly purpura)	80
GI symptoms (nausea, abdominal pain, GI bleeding)	24
CNS symptom (focal neurologic deficits, progressive dementia)	11
Retinal emboli (Hollenhorst plaque on fundoscopy)	19
Fevers	Uncommon
Laboratory findings [reference]	
Microscopic hematuria [38, 39]	53
Mild proteinuria (rarely nephrotic associated with a secondary collapsing FSGS or accelerated hypertension) [39, 40]	9
Eosinophiluria (by Hansel's stain)	88
Peripheral blood eosinophilia [41]	48–88%
Hypocomplementemia [41]	<15–12
Various markers of ischemic organ injury (elevated creatinine kinase, amylase/lipase, transaminases)	Not uncommon
Elevated erythrocyte sedimentation rate and/or C-reactive protein	Very common
Renal artery stenosis by Doppler or angiography [38, 42]	44

CK, creatine kinase; CNS, central nervous system; FSGS, focal and segmental glomerulosclerosis; GI, gastrointestinal.
Unless otherwise indicated, frequency data come from combining three case series of *clinically significant* kidney disease totaling 171 patients.
Source: Belenfant et al. [38], Thadhani et al. [39], and Scolari et al. [42].

Course and Management

Three patterns of disease evolution are apparent in atheroembolic renal disease [44]. An acute course (20–30% of cases) resulting from a massive embolic load is characterized by an abrupt deterioration in kidney function and multiorgan involvement within a week after the inciting event. More common, however, is the subacute course (56%), which represents repeated smaller embolic showers and their subsequent inflammatory endothelial response. Thus, there is a stepwise deterioration in kidney function averaging 3–8 weeks. The third entity involves a slowly progressing renal insufficiency secondary to chronic ischemia mimicking hypertensive nephrosclerosis or ischemic renovascular disease. This is often underdiagnosed because of the paucity of systemic organ involvement and the failure to obtain kidney biopsy.

Progression to dialysis dependence occurs in one-third of the patients who survive the initial insult. Preexisting CKD and a history of significant claudication confers greater risk for this outcome. Some mild improvement in

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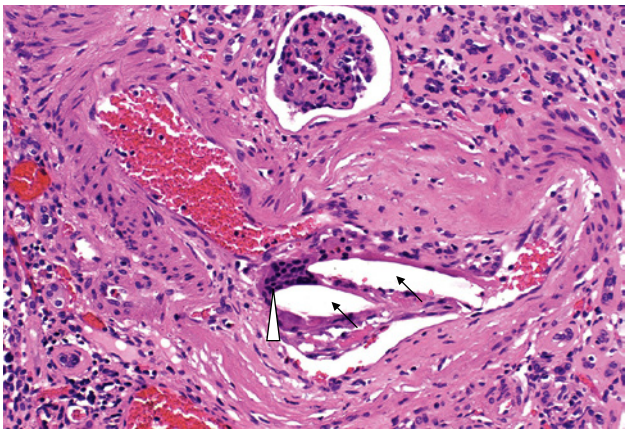

Figure 12.2 Renal atheroembolic disease, hematoxylin and eosin stain. Arrows represent cholesterol clefts remaining in an intralobular artery where lipid had been present prior to the fixation process. The early inflammatory arteritis composed of eosinophils, neutrophils, and macrophages is later replaced by a giant cell foreign body reaction (arrowhead), intimal proliferation, and fibrosis. *Source:* Courtesy of Helen Liapis MD, Washington University School of Medicine.

kidney function can occur with time, from progressive hyperfiltration by the remaining nephrons. As a result, 21–32% of patients on chronic dialysis from atheroembolic renal disease can recover enough kidney function to stop dialysis [38, 41, 45]. Early studies revealed a grim outcome for patients with acute, multivisceral atheroembolic disease, with 1-year survival rates of 13–36% [39, 46]. Death usually occurs from cardiac ischemia, heart failure, stroke, or gastrointestinal ischemia with malnutrition [39, 44, 45]. An aggressive supportive regimen specifically targeting these mechanisms of mortality was prospectively evaluated in a population with acute multivisceral atheroembolic disease [38].

The principles of treatment for atheroembolic disease are intended to decrease the ischemic damage and prevent recurrent embolization. The mainstay of treatment is often preventative and supportive. The major preventative measures include avoiding anticoagulation (if feasible after carefully considering risks and benefits) and avoiding any further invasive procedures that might trigger further plaque disruption. To delay progression, blood pressure control and judicious use of statins and renin-angiotensin-aldosterone system (RAAS) blockers should be considered. Nutritional replacement, including parenteral replacements, may be needed in settings of intestinal ischemia. With advanced kidney failure, dialysis should be considered.

Several adjunctive therapies to improve renal outcome have been attempted in cases of atheroembolic renal disease. Belenfast et al. [38] determined that low-dose corticosteroids (0.3 mg/kg of prednisone) improved nutritional intake and symptoms in 18 patients with recurrent atheroembolic disease. Other studies have used high doses of steroids with variable benefits. Prospective studies have shown beneficial effects of statins in the progression to end stage renal disease (ESRD). Observations have shown that statins help to decrease lipid level, stabilize plaques, and are anti-inflammatory. Lipoprotein aphesis is known to significantly reduced cholesterol levels and has been recommended for use in patients with high risk [47, 48]. Surgical procedures such as endoluminal stenting could provide a definitive treatment, although this is often not feasible because the disrupted plaque is difficult to identify or the patient may be too fragile to undergo any surgical intervention. If endovascular procedures are required in high-risk patients, strategies such as "no-touch" techniques to minimize plaque disruption, and embolic protection devices may help to prevent the development of atheroembolic disease [49–51].

Atheroembolic disease generally has poor prognosis as it is associated with multiorgan system involvement, often with irreversible damage. About 30–55% of patients with acute/subacute onset of kidney failure need dialysis, of whom 21–28% have renal recovery and 23–32% progress to ESRD. Preexisting CKD and hypertension are determinants for progression to ESRD [39, 42].

AKI Associated with Malignancies

Cast Nephropathy

Definitions and Etiology

Multiple myeloma (MM) is a hematological malignancy characterized by abnormal proliferation of monoclonal plasma cells in the bone marrow. It is the second most common hematological malignancy, diagnosed in approximately 13% of all hematological malignancies, and the American Cancer Society estimates a lifetime risk of 0.76% in the United States. The definition of renal impairment in MM, as defined by the International Myeloma Working Group (IMWG) criteria, includes a serum creatinine level of ≥2 mg/dl or creatinine clearance of <40 ml/min [52]. Based on these criteria, kidney involvement can range from 20% to 30% of patients with MM. AKI associated with plasma cell dyscrasias can result from (i) prerenal AKI secondary to hypercalcemia and/or volume depletion; (ii) glomerular disease from light-chain deposition disease or amyloidosis; and (iii) tubulointerstitial disease from cast nephropathy and drug-induced AKI (from intravenous bisphosphonates). Other etiologies of AKI in MM include glomerular diseases (e.g. membranoproliferative glomerulonephritis, light-chain deposition disease, amyloidosis) associated with paraproteinemia and, to a

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lesser extent, tumor lysis syndrome (TLS), which will be discussed separately. In the updated Diagnostic Criteria and Staging System for MM only light-chain cast nephropathy is defined as myeloma defining illness [53].

Myeloma cells synthesize free light chains (FLCs) which are freely filtered by the glomerulus. These proteins are then reabsorbed by the megalin and cubulin receptors of the proximal convoluted tubule [54]. When the filtered load exceeds the maximal reabsorption of the receptors, they are excreted in the urine and referred to as Bence–Jones proteins. The FLCs may interact with Tamm–Horsfall protein (THP) causing tubular obstruction inducing inflammation and resultant interstitial nephritis and fibrosis [55].

Clinical Features and Laboratory Findings

Cast nephropathy is suspected when patients present with rapidly declining kidney function in the setting of FLCs detected by plasma or urine immunofixation or by serum FLC measurement. IMWG recommends a 24-hour urine protein electrophoresis and a serum FLC assay. In the setting of reduced kidney function, the serum FLC may be elevated, but not in a clonal pattern. If a clonal serum FLC is >500 mg/l, quantitative urinary albumin excretion should be assessed. In glomerular causes of AKI, the predominant urinary protein is albumin; but when albumin ≤10% of total urinary protein, the diagnosis is likely to be cast nephropathy and kidney biopsy can be avoided. If quantitative urinary light chains are <1 g/day, an alternate diagnosis should be considered and a kidney biopsy may be warranted.

The definite diagnosis is obtained from kidney biopsy. On light microscopy, cast nephropathy is manifested by the presence of large lamellated eosinophilic casts in the distal convoluted and collecting tubules. Features of interstitial inflammation and nephritis are also seen (Figure 12.3). The casts are comprised primarily of monoclonal light chains but also contain albumin, THP, fibrin, and polyclonal light chains.

Course and Treatment

Treatment of cast nephropathy includes general measures and disease-specific treatments. General measures include adequate volume expansion, correction of hypercalcemia and hyperuricemia, discontinuation of potential nephrotoxic medications, such as NSAIDs and angiotensin converting enzyme inhibitors (ACEI), and angiotensin receptor blockers (ARBs), loop diuretics, and avoidance of iodinated intravascular contrast.

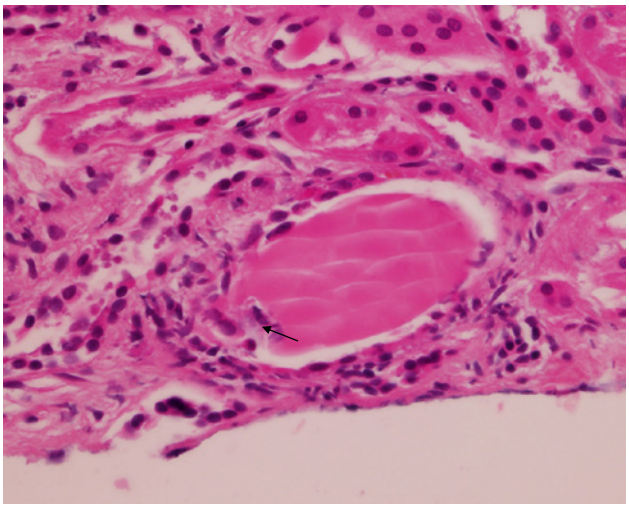

Figure 12.3 Myeloma cast nephropathy, with hematoxylin and eosin stain. There is a characteristic eosinophilic, "corrugated paper" appearance of this cast that is adherent to the wall of the tubule. There is resulting tubular cell toxicity and inflammation, with an interstitial infiltrate and cells engulfing the cast at its point of adherence (arrow). *Source:* Courtesy of Helen Liapis, MD, Washington University School of Medicine.

Newer chemotherapeutic agents have increased overall survival in MM. Renal protective chemotherapy with thalidomide or bortezomib aims at rapidly decreasing FLC concentrations. Bortezomib-based regimens have been associated with improved kidney function and are the treatment of choice [54, 56, 57]. A Cochrane meta-analysis with 16 studies and 5626 patients suggested better survival rates and longer time without progression with bortezomib. Metabolized by liver, it can be safely administered to patients with kidney failure. Thalidomide and lenalidomide are also targeted chemotherapy for MM. In one study of 133 patients, renal recovery was noted in 77%, 55%, and 43% of patients treated with bortezomib, thalidomide, and lenalidomide, respectively [57]. In a multivariate analysis, bortezomib had superior results with respect to probability of response as well as the median response time compared to the other two agents. A retrospective cohort study analyzing autologous stem cell transplant and renal recovery showed that 14 out of 15 patients with advanced kidney failure, who received transplant remained dialysis dependent despite hematological recovery; however, it is important to note that having kidney failure did not exclude them from this curative therapy [58].

The idea that therapeutic plasma exchange (TPE) would be effective in removal of FLC stems from the fact that FLC have small molecular masses. Trials evaluating the role of TPE in cast nephropathy were performed before the advent of newer bortezomib-based regimens. Burnette et al. analyzed 14 patients from 2004 to 2010 who

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received TPE and bortezomib, and showed full renal recovery in 43% of patients in 6 months [59]. Given the lack of sufficient data from current literature, the role of TPE in cast nephropathy remains nebulous and cannot be recommended. Two recent trials – EuLite and MYRE – evaluated the role of high-cut-off hemodialysis (HCO-HD) along with concomitant chemotherapy in the treatment of biopsy confirmed cast nephropathy [60, 61]. In both trials, the primary outcome of dialysis independence at 30 days was not significantly different between the HCO-HD arm versus the control groups. In the MYRE study, dialysis independence at 6 months was superior to conventional treatment alone (35% vs. 57%, $P = 0.04$) [61, 62]. It should be noted that there was a higher incidence of death due to infections in the HCO-HD arm in the MYRE study, but 11% of patients in the HCO-HD arm compared to 4% in the conventional HD arm had infection at baseline. There was no difference in infectious complications in the EuLite trial. HCO-HD is not FDA approved for treatment of cast nephropathy in the United States. The IMWG recommends that HCO-HD can be considered as an adjunct to bortezomib-based chemotherapy in patients with MM and severe kidney impairment (grade B evidence) [63].

AKI Secondary to Bisphosphonate Therapy

Intravenous bisphosphonates are widely used in the treatment of hypercalcemia of malignancy. Both zoledronate and pamidronate have been associated with AKI. Acute tubular injury and collapsing focal segmental glomerulosclerosis have been described [64]. The 2015 European Myeloma network guidelines [65] recommend measuring creatinine clearance, serum electrolytes, and urine albumin in all patients receiving bisphosphonates (grade 1A). These drugs should be avoided if CrCl <30 mg/dl (grade 1A). Dose reduction is necessary for zoledronate with no change in infusion time (grade1A) whereas pamidronate should be given over a 4-hour infusion (grade 1C). Clodronate can be used as alternative in patients with CrCl >12 ml/min (Grade 2C). To prevent hypocalcemia, calcium and vitamin D supplementation should be administered. (Grade 1A).

Tumor Lysis Syndrome

TLS is one of the most common hematological emergencies. TLS describes an array of biochemical abnormalities secondary to cell lysis that occur spontaneously or after initiation of cytotoxic chemotherapy. The cell damage releases intracytoplasmic molecules, including proteins, electrolytes, and nucleic acids, into systemic circulation, causing hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia. Multiorgan failure, including AKI, life-threatening cardiac arrhythmias, seizures, and death, is known to occur. The Cairo–Bishop diagnostic criteria for laboratory and clinical TLS are shown in Table 12.4.

TLS is most commonly described in malignancies with large tumor burden: non-Hodgkin lymphoma, especially Burkitt's lymphoma, acute and chronic leukemias, and MM [67–69]. Certain solid organ tumors like germ cell tumors, neuroblastoma, breast, and small cell lung cancer, especially when associated with widespread metastasis, also predispose to TLS. Although previously described with chemotherapy, other forms of treatment, including corticosteroids, tamoxifen, radiotherapy, and newer targeted therapy with biologicals, can also cause TLS. Elevated serum lactate dehydrogenase (LDH) is an additional risk factor predisposing to TLS [70].

Pathophysiology

Uric acid is the end product of the metabolism of purine nucleotides in humans and higher primates. Uric acid is freely filtered by the glomerulus, but in contrast to previous studies, recent data suggest that our understanding of the tubular handling of uric acid is incomplete [71]. Uric acid is actively reabsorbed and secreted at the proximal tubule via complicated interplay among various transport pathways involving urate transporter 1 (URAT1), glucose transporter 9 (GLUT9), and organic anion transporters (OATs), among others [71]. Uric acid crystallization occurs when concentration in the tubules exceeds the solubility, and this usually occurs in setting of low urine volume and acidic

Table 12.4 Cairo–Bishop definition of tumor lysis syndrome [66].

Laboratory tumor lysis syndrome (LTLS)	Two or more occurring within 3 days before or 7 days after chemotherapy • Uric acid ≥ 8 mg/dl or 25% increase from baseline • Potassium ≥ 6 mEq/dl or 25% increase from baseline • Phosphorus ≥ 4.5 mg/dl or 25% increase from baseline • Calcium ≤ 7mg/dl or 25% decrease from baseline
Clinical tumor lysis syndrome (CTLS)	LTLS with one or more of the following: serum creatinine ≥1.5 upper limit of normal cardiac arrhythmia or death seizures

Source: Cairo and Bishop [66].

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pH. Hyperphosphatemia results when tumor cells with high metabolic rates and turnover die, releasing high levels of intracellular phosphorus into bloodstream, overwhelming the kidney's capacity to eliminate it. In spontaneous TLS, severe hyperphosphatemia is less likely, since the surviving tumor cells, with their high metabolic rate, rapidly recycle released phosphate. Phosphorus binds with calcium cations, causing hypocalcemia, and calcium phosphate complexes can precipitate in the kidney and other tissues. Patients can develop signs and symptoms of hypocalcemia, including tetany and seizures. AKI in TLS is thus thought to be secondary to uric acid and calcium phosphate crystal nephropathy. In addition to the crystalline pathway, vasoconstriction and inflammation also play a role in the pathogenesis of AKI.

Management

The management of TLS can be divided into preventative and therapeutic measures. Patients who are at high risk for TLS should be closely monitored for electrolyte abnormalities and metabolic acidosis. General measures such as avoidance of nephrotoxic drugs including NSAIDs and radiocontrast is necessary. Volume expansion with the use of crystalloids to maintain a urine output of ≥2 ml/kg/h [72] helps ensure adequate glomerular filtration and high tubular flow rates, thereby enhancing excretion of uric acid, phosphorus, and potassium, and minimizing the risk of uric acid and calcium phosphate precipitation. Even though uric acid is soluble in alkaline urine, urine alkalization can decrease the solubility of calcium phosphate and increase the risk for calcium phosphate nephropathy. Ideally this should be initiated 2 days prior to the initiation of chemotherapy. Also, alkalosis leads to increased binding of calcium to albumin, reducing ionized calcium, and hence routine alkalization of urine is not recommended [69, 72].

Allopurinol (which gets converted to oxypurinol in vivo) is a competitive inhibitor of the enzyme xanthine oxidase. Oxypurinol competes with purines and decreases their conversion to uric acid. Hence it is most effective in the prevention of hyperuricemia [73]. However, the drug also inhibits the conversion of xanthine to uric acid, hence there is a risk of formation of xanthine crystal in the renal tubules [70]. A large study including 1172 adults and children, treated with intravenous allopurinol, was found to decrease uric acid level in 57% of adults when used for treatment and by 93% when used prophylactically [73]. Febuxostat is a newer xanthine oxidase inhibitor that is metabolized in the liver and hence can be used safely in patients with kidney insufficiency [70]. Rasburicase is a recombinant uricase enzyme that converts uric acid into allantoin, which is 5–10 times more soluble in urine than uric acid. The dosing approved by FDA is 0.2 mg/kg in a 30-minute intravenous infusion once daily for up to 5 days [74, 75]. Rasburicase does not require renal dosing. It can cause methemoglobinemia and hemolysis in patients with glucose-6-phosphate dehydrogenase deficiency hence all patients should be checked for enzyme activity prior to starting rasburicase [76].

Most patients with AKI will not require dialysis and will recover kidney function, although patient and renal prognosis may be worse with spontaneous TLS. Before the availability of rasburicase, hemodialysis was often initiated early in order to rapidly reduce uric acid levels, with a 50% reduction occurring after 6 hours of hemodialysis (clearance of 70–145 ml/min) [77]. Rasburicase results in more prompt reduction of uric acid and eliminates this indication for RRT. However, when significant hyperphosphatemia is present, early RRT may still be required along with noncalcium-based phosphate binders to prevent further phosphate precipitation and/or hypocalcemia. Treatment of hypocalcemia with intravenous calcium without first lowering the phosphorus should be reserved for symptomatic patients or those with EKG changes as calcium administration in the setting of hyperphosphatemia can cause calcium phosphate precipitation. Even though phosphorus clearance is high (approximately 50–90 ml/min) with intermittent hemodialysis (IHD), the short duration of IHD (usually 4 hours/day) is not sufficient to achieve negative phosphorus balance. The longer duration of treatment offered by continuous or prolonged intermittent RRT is more effective for phosphorus clearance and should be considered for patients with TLS [78].

Crystalline Nephropathies

Definition, Etiology, and Pathogenesis

Crystalline nephropathies describe the kidney injury that results from the intratubular precipitation of substances. Uric acid nephropathy was discussed earlier and this section will focus on other crystalline nephropathies. Intratubular crystal formation and deposition of a substance is promoted by three mechanisms: (i) high concentrations of the offending agent in the tubular fluid; (ii) prolonged intratubular transit time; and (iii) decreased solubility [79]. The first two mechanisms occur in the setting of decreased effective circulating volume, which results in proximal tubular sodium and water reabsorption, resulting in high concentration of the offending agent in the distal tubule along with decreased distal flow rates. Underlying CKD is an important risk factor for the crystalline

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nephropathies. In CKD, the amount of compound excreted per remaining functioning nephron is increased, raising the likelihood of intratubular precipitation. The third mechanism, decreased solubility, is often dependent on the distal tubular fluid pH. Compounds with pKa < 7, such as uric acid, calcium oxalate, sulfonamides, methotrexate, and triamterene, tend to precipitate in acidic urine, whereas compounds with pKa > 7, such as indinavir and calcium phosphate, tend to precipitate in alkaline urine. Once crystals are formed in the tubular lumen, the tubular epithelial cells attempt to phagocytose and digest the crystals with proteolytic enzymes, resulting in direct cellular toxicity and necrosis. Crystal-induced toxicity can also lead to significant peritubular inflammation, sometimes mimicking AIN [80, 81].

Inadequate dose reduction for the level of kidney function is frequent, leading to increased drug exposure. The clinical contexts in which the more common crystalline nephropathies occur are summarized in Table 12.5. Besides TLS, other causes of crystalline nephropathy include calcium oxalate, acyclovir, sulfonamides, methotrexate, indinavir, and triamterene. Ethylene glycol intoxication is discussed separately due to its unique pathogenic mechanisms and treatment strategies.

Clinical Features

Extensive crystal deposition results in pain from distention of the renal capsule and is similar in nature to the pain due to nephrolithiasis. Oliguria is uncommon unless there is bilateral obstruction. In certain cases (especially with indinavir and sulfonamides), macroscopic lithiasis and its characteristic presenting symptoms can exist alone or concomitantly with intratubular crystal nephropathy [88, 90]. Precipitation of calcium with phosphates and oxalates can lead to symptomatic hypocalcemia, leading to paresthesia, tetany, and lethargy. High levels of acyclovir seen in AKI can lead to hallucinations, delirium, and myoclonus. Methotrexate can cause stroke-like symptoms (not dose-related) as well as nausea, rash, and mucositis (usually dose-related).

Laboratory Findings

Urinalysis and microscopic examination of the urine sediment are often nonspecific, generally revealing hematuria, pyuria, and mild proteinuria. Although the offending substances have unique crystal morphologies on urine microscopy, finding urine crystals may not be independently diagnostic. Urine microscopic images of some crystals are shown in Figure 12.4a–e. Absence of crystals on urine microscopy can occur when there is tubular obstruction and hence does not rule out crystal nephropathy. Conversely, the presence of crystals does not prove their pathogenic role because calcium oxalate, calcium phosphate, and uric acid crystalluria may be seen in normal individuals. Furthermore, crystalluria has been found in patients without AKI in frequencies varying from 100% of healthy individuals receiving a single 100-mg dose of triamterene and ascorbic acid (for urinary acidification) to 17% of all patients taking indinavir [90].

Ultrasound may reveal bilaterally enlarged and echogenic kidneys and can identify concomitant macroscopic lithiasis. Kidney biopsy is sometimes required to make a definitive diagnosis. Light microscopy may reveal crystalline deposits (usually in the distal tubules), with a surrounding interstitial infiltrate that may contain giant cells as part of a foreign body reaction. Evidence of ATN can also be present, secondary to direct tubular cell toxicity. Polarized microscopy may demonstrate birefringence, depending on the offending agent (Figure 12.5a,b). A summary of the characteristic laboratory findings is outlined in Table 12.5.

Course and Management

In most cases of crystalline nephropathy, the renal prognosis is excellent if further exposure to the precipitating substance can be avoided. In drug-related crystalline nephropathies, recovery of kidney function is expected to occur within days to weeks after cessation or dose reduction of the offending drug. An exception is the use of phosphate-containing colonoscopy preparation, causing phosphate nephropathy. Although there was likely selection bias for more severe cases, the largest series characterizing this disease found that none of 21 affected patients returned to their previous level of kidney function and four progressed to require chronic dialysis [82].

The mainstay in preventing crystalline nephropathy is avoidance of the two most frequent predisposing factors: volume depletion and drug overdosing relative to the level of kidney function. Establishing a brisk urine output (e.g. 100–150 ml/h or greater) in high-risk patients is extremely important. For substances with pKa < 7 (e.g. uric acid, calcium oxalate, sulfonamides, methotrexate, triamterene) urinary alkalization by administering intravenous isotonic bicarbonate solutions or oral citrate can be considered. Urine pH should be periodically followed to ensure an appropriate level of alkalization to achieve pH > 7.15. Excess alkalization of urine can lead to precipitation of calcium phosphate crystals and should be avoided. Acetazolamide may be added if a metabolic alkalosis ensues. Attempting to acidify the urine to increase the solubility of weakly basic compounds is dangerous

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Table 12.5 Causes of crystalline nephropathy, their distinctive clinical and laboratory features, and strategies for prevention and treatment.

Inciting agent [reference]	Clinical context	Laboratory findings	Prevention and treatment	Disease course
Phosphate [82]	TLS, especially post treatment form Phosphasoda bowel prep with risk increased by ACEi/diuretic use, advanced age, CKD, and/or female gender • Rhabdomyolysis (rare)	Crystalluria with weakly birefringent, long prisms, often in rosettes Hyperphosphatemia out of proportion to kidney insufficiency Hypocalcemia Hyperkalemia out of proportion to kidney insufficiency High LDH in TLS, rhabdomyolysis, and hemolysis Kidney biopsy: von Kossa-positive crystals	*Prevention* Forced diuresis[a] Noncalcium-based phosphate binders *Treatment* Forced diuresis[a] Noncalcium-based phosphate binders Avoid treatment of hypocalcemia unless symptomatic or ECG changes present Consider early initiation of RRT, especially CRRT	Incidence of CKD higher in cases caused by phosphasoda
Uric acid [83, 84]	TLS, especially spontaneous form Rhabdomyolysis (rare) HGPRT deficiency (rare)	Crystalluria with brownish, strongly birefringent, rhomboid plates, rosettes, or needles UA >15 mg/dl (peaking 2–3 days after initiation of treatment in TLS) Urine UA/urine Cr >1 (<0.75 suggests alternative diagnosis) Hyperkalemia out of proportion to kidney insufficiency Elevated LDH in TLS and rhabdomyolysis	*Prevention* Forced diuresis[a] Allopurinol or rasburicase *Treatment* Rasburicase RRT (if rasburicase not available)	Full renal recovery expected in the absence of other insults; higher mortality in spontaneous TLS
Oxalate [85, 86]	EG poisoning High-dose i.v. ascorbic acid–xylitol–sorbitol infusions (rare) Primary hyperoxaluria (rare)	Crystalluria with birefringent monohydrate needles or dihydrate envelope shapes appearing >4 h after EG ingestion Hypocalcemia In EG poisoning, osmolal gap >10 mOsm/l and detectable serum and urine EG early with subsequent development of severe anion gap acidosis Kidney biopsy: silver nitrate/rubeanic acid stain-positive crystals	*Prevention* Forced diuresis[a] Consider urine alkalinization Fomepizole for high-risk EG ingestion[b] (ethanol is second line) i.v. thiamine, magnesium, and pyridoxine in alcoholic patients *Treatment* Forced diuresis[a] Consider urine alkalinization Avoid treatment of hypocalcemia unless symptomatic or ECG changes present Fomepizole (ethanol is second line) if EG level >20 mg/dl Early initiation of RRT, especially if EG >50 mg/dl and renal insufficiency or acidosis present	Full renal recovery occurred in 6/9 patients; duration and severity of AKI is predicted by severity of acidosis at presentation

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Acyclovir [87]	Associated with intravenous dosing 11% develop AKI with high-dose rapid i.v. bolus	Crystalluria with birefringent needles with occasional engulfment by WBC	*Prevention* Forced diuresis[a] Increase time of i.v. infusion to 1 hour *Treatment* Forced diuresis[a] Decreasing the dose is sufficient in 40–50% of patients	Full renal recovery expected
Indinavir [88]	18.6% develop AKI, especially with longer treatment, smaller body size, and concurrent TMP-SMX	Crystalluria with birefringent plates, fans, or starbursts Isosthenuria common CT with i.v. contrast shows wedge-shaped perfusion defects in up to 50%	*Treatment* Forced diuresis[a] Urologic consultation if concomitant macroscopic obstruction present (not uncommon)	AKI is easily reversible as opposed to the slowly progressive injury seen in indinavir-induced AIN
Methotrexate [89]	2–4% develop AKI with high-dose i.v. therapy; increased risk in older patients and with concomitant use of NSAID or other highly protein-bound drugs which increase free methotrexate levels	Crystalluria with amorphous yellow casts High serum methotrexate level Anemia, leukopenia, or thrombocytopenia possible	*Prevention* Forced diuresis[a] Urinary alkalinization to pH ≥ 8 *Treatment* Forced diuresis[a] Urinary alkalinization to pH ≥ 8 Leucovorin rescue ± thymidine for extrarenal toxicity until methotrexate level <0.05 μmol/l Consider carboxypeptidase G2 (>98% fall in levels by 15 minutes) vs. daily 6-hour high-flux hemodialysis (clears drug in 5.5 days)	Median time to renal recovery to 2–3 weeks
Sulfonamides [90]	Usually with high-dose therapy More common with sulfadiazine (1.9–7.5% incidence in AIDS patients) Low serum albumin may increase risk from higher free drug levels	Crystalluria with variable shapes from shocks of wheat to spheres Positive lignin test (orange urine upon mixing with 10% hydrochloric acid) Densities in parenchyma and in collection system on ultrasound are common	*Treatment* Forced diuresis[a] Urine alkalinization to pH > 7.1 Dose reduction usually sufficient Urologic consultation if macroscopic obstruction present (not uncommon)	Full renal recovery is prompt, sometimes within hours, but median 6 days
Triamterene [79]	Rare; must distinguish from the much more common AIN, or AKI with concomitant NSAID use	Crystalluria with birefringent orange casts and spheres Hyperkalemia out of proportion to renal insufficiency	*Treatment* Forced diuresis[a] Urine alkalinization to pH > 7.5 May require urologic consultation for the more common triamterene stone if obstructed	Full renal recovery is expected

CRRT, continuous renal replacement therapy; CT, computerized tomography; ECG, electrocardiogram; EG, ethylene glycol; HGPRT, hypoxanthine-guanine phosphoribosyl transferase; i.v., intravenous; LDH, lactate dehydrogenase; TLS, tumor lysis syndrome; TMP-SMX, trimethoprim-sulfamethoxazole; UA, uric acid.

[a] Forced diuresis refers to aggressive hydration with judicious use of diuretics to achieve and maintain brisk urine flow rate.

[b] Patients at high risk for organ dysfunction in EG poisoning are those with serum EG of >20 mg/dl, OR with known recent ingestion of EG with osmolal gap >10 mOsm/l, OR strong suspicion of recent ingestion and two of the following: pH <7.3, HCO_3 < 20 mEq/l, osmolal gap >10 mOsm/l, and urinary oxalate crystals [85].

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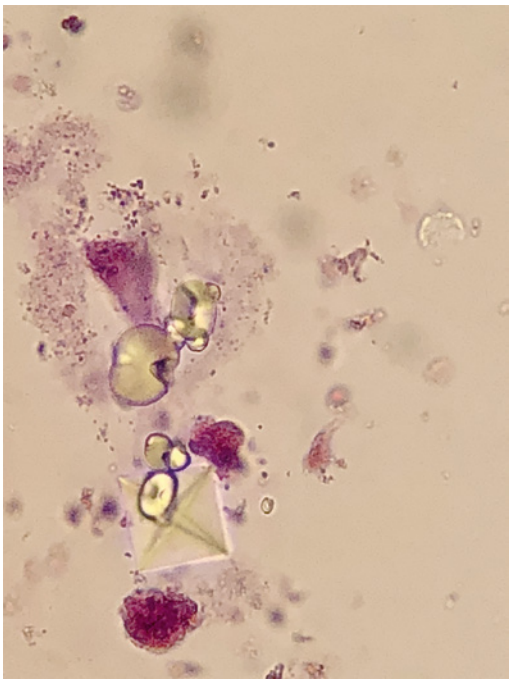
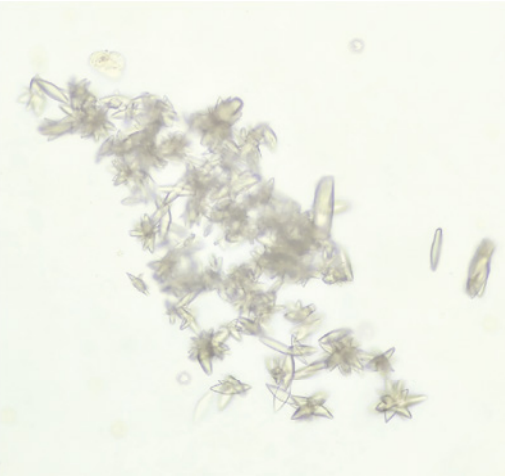
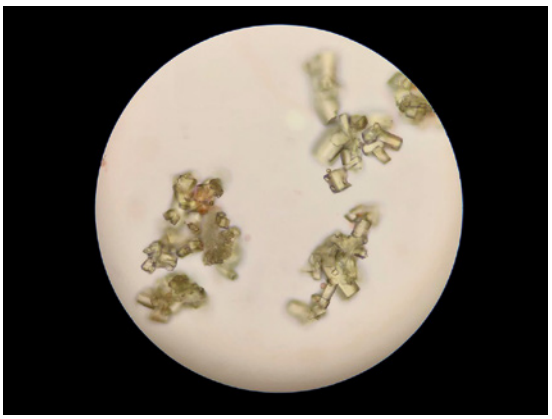


(a)

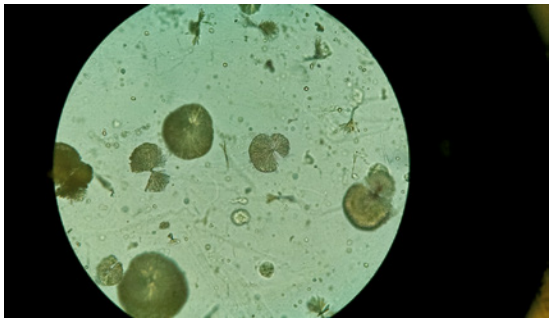


(b1)

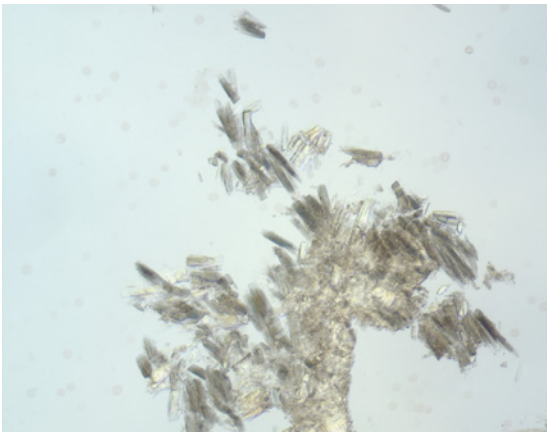


(b2)

(c)



(d)



(e)

Figure 12.4 (a)–(e) Crystals on urine microscopy. (a) Calcium oxalate crystals may appear in the monohydrate (dumbbell shaped) and dihydrate (envelope shaped) form as shown here (brightfield illumination, original magnification 400×). (b) Uric acid crystals can be seen in various forms. The rhombic and rosette forms are shown in 4B:1 and the barrel-shaped forms are shown in 4B:2 (brightfield illumination, magnification 400×). *Source:* Images (a), 4B:1 and 4B:2: courtesy of Jay Seltzer MD, St. Louis Kidney Consultants, St. Louis, MO. (c) Acyclovir crystals are typically needle shaped, as shown here (brightfield illumination, magnification 400×). (D) Sulfadiazine crystals can appear as striated shells or "shocks of wheat" (brightfield illumination, magnification 400×). *Source:* Images (c) and (d): courtesy of José Antonio Tesser Poloni, Urinalysis Section – Carlos Franco Voegeli Clinical Analysis Laboratory, Santa Casa de Misericórdia de Porto Alegre, Brazil. (e) Indinavir crystals are shown here as rectangular plates with irregular borders and occasional tapering (brightfield illumination, magnification 400×).

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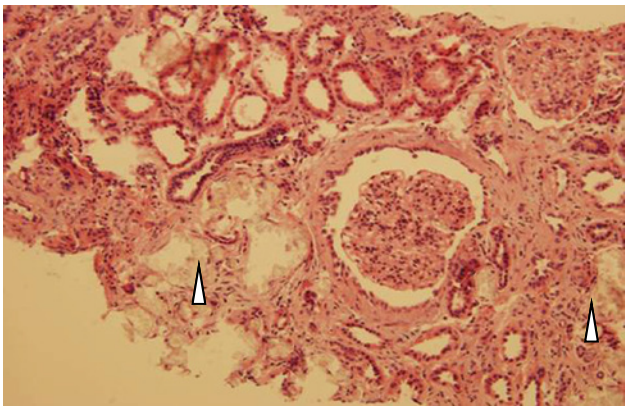
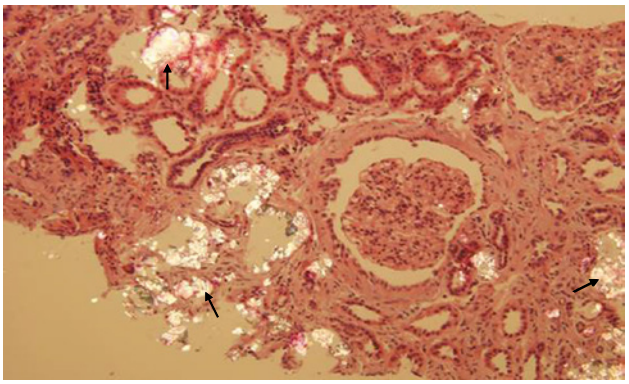


(a)



(b)

Figure 12.5 (a) and (b) Oxalate nephropathy, hematoxylin and eosin stain. This patient developed renal failure in the setting of primary hyperoxaluria. (a) Note the distortion of the tubular architecture associated with intratubular deposits of calcium oxalate (arrow heads). There is an interstitial infiltrate along interstitial fibrosis consistent with disease chronicity. (b) Under polarized light the deposits exhibit birefringence (black arrows). *Source:* Courtesy of Dr. Rosa Davila, Washington University School of Medicine.

and not recommended. These preventive strategies are based on underlying pathophysiologic mechanisms, and evidence proving reduced renal complications with these measures is lacking, except perhaps with high-dose methotrexate administration.

Treatment of established AKI consists of discontinuation of the drug and, if nonoliguric and in the absence of volume overload, applying many of the same principles used in prevention: forced diuresis (aggressive volume expansion with judicious use of diuretics) and, for weak acids, urinary alkalization. In the setting of AKI, moderate to large doses of diuretics may be required to establish adequate urine flow, and care must be taken with bicarbonate loading to avoid profound alkalosis. Additionally, early initiation of RRT can rapidly decrease the concentration of some inciting agents (e.g. phosphate, oxalate).

High-dose methotrexate causing AKI can in turn increase its serum levels, causing acute systemic methotrexate toxicity from decreased urinary clearance. In addition to large volume hydration and forced alkaline diuresis, leucovorin can be administered to decrease the cytotoxicity of the drug. Glucarpidase (carboxypeptidase) was approved in 2012 for MTX concentrations >1 umol/l to decrease its systemic toxicity if the above measures are unsuccessful in bringing down the levels [91]. Studies have shown daily hemodialysis with high flux dialyzers and sessions of 4–6 hours in duration are effective in removing methotrexate [89]. Again, evidence for improvement in renal outcome with these maneuvers is lacking. See Table 12.5 for details on specific management strategies.

Ethylene Glycol Poisoning

Ethylene glycol (or antifreeze) is metabolized by the hepatic alcohol dehydrogenase into four toxic metabolites: glycoaldehyde, glycolic acid, glyoxylic acid, and oxalic acid. Accumulation of organic anions (glycolate, glyoxylate, and oxalate) leads to a severe anion gap metabolic acidosis. These compounds, especially glycolic acid, are direct cellular toxins and cause multiorgan dysfunction, including cardiotoxicity, ATN, and nervous system depression. In addition, oxalate precipitates with calcium in several tissues, including the renal tubules, causing crystalline nephropathy (Figure 12.4a,b).

The clinical manifestations of ethylene glycol intoxication evolve over time as the alcohol is metabolized. During the first 30 minutes to 12 hours, ethylene glycol causes inebriation, with progression to seizures or coma. Twelve to 36 hours post ingestion, profound acidosis ensues as the concentration of the organic acid increases, leading to Kussumals breathing and cardiorespiratory failure. Twenty-four to 72 hours later, the oxalate end product accumulates in tissues, including the kidneys, resulting in AKI. The timeline is extended when there is co-ingestion of ethanol, which acts as a competitive inhibitor of alcohol dehydrogenase. The focus of treatment in ethylene glycol toxicity involves decreasing the concentration of its toxic metabolites. This can be achieved by (i) reducing organic acid formation by use of competitive alcohol dehydrogenase inhibitors, such as fomepizole or ethanol; (ii) increasing metabolite clearance through early initiation of RRT, and (iii) conversion to less toxic metabolites by cofactor supplementation like thiamine and pyridoxine (Table 12.5). Other causes of oxalate nephropathy include enteric hyperoxaluria after bariatric surgeries and primary oxaluria.

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Renovascular Etiologies of Acute Kidney Injury

Renal Artery Thrombosis and Renal Infarction

Acute renal artery thrombosis (RAT) is a rare clinical entity characterized by acute onset of abdominal or flank pain, nausea, vomiting, hematuria, hypertension, and even more rarely AKI. Most common causes of renal infarction are cardioembolic, although the percentage involvement varies with different studies, ranging from 18% to 55.7% [92–95]. Renal artery injury following blunt abdominal trauma and hypercoagulable states like nephrotic syndrome (NS), antiphospholipid antibody syndrome, paroxysmal nocturnal hemoglobinuria, as well as systemic malignancies can predispose to RAT as well. In one large case series, AKI developed in 21% of patients with renal infarction [95]. AKI is unusual with unilateral involvement unless there is baseline CKD. CT scan with intravenous contrast is the imaging modality of choice in suspected RAT, however intravenous contrast should be used with caution in those with kidney injury. Magnetic resonance angiography is another option, but exposure to gadolinium is associated with nephrogenic systemic fibrosis in patients with CKD. For patients with GFR <30 ml/min, including those undergoing dialysis, it is generally recommended that gadolinium exposure be avoided if possible and alternative imaging modalities be pursued [96]. Management of RAT involves systemic anticoagulation with heparin and a bridge to warfarin to maintain therapeutic INR between 2 and 3. There are limited data regarding use of direct oral anticoagulants in this setting. Endovascular procedures like stenting and thrombolysis have favorable outcomes when performed early [97]. Prognosis depends on severity of kidney injury and underlying comorbidities. In the largest series, mortality was 5% and 2% progressed to ESRD [95].

Renal Vein Thrombosis

Renal vein thrombosis (RVT), either unilateral or bilateral, is an extremely rare cause of AKI. The common etiologies are NS and other hypercoagulable states, such as antiphospholipid antibody syndrome. Of all the causes of NS, patients with membranous glomerulonephritis have the highest prevalence of RVT (37%) [98]. In a case series, low serum albumin of less than 2.8 g/dl, rather than proteinuria, was found to have increased risk for thrombotic episodes [99]. Selective renal venogram is considered the gold standard for diagnosis, but it is not routinely performed due to a high risk for contrast-induced AKI as well as vascular complications. In one series, computerized tomography had a sensitivity of 92% and specificity of 100%. A series investigating Doppler ultrasonography revealed a sensitivity of 85% and specificity of 56%, but this modality is heavily operator dependent [98]. Magnetic resonance imaging can also be used, although adequate studies have not evaluated this modality.

Treatment of RVT involves conventional anticoagulation with intravenous heparin and warfarin sodium. Use of thrombolytics in RVT has been reported, but given the risk for bleeding their use should be considered only in patients with severe bilateral RVT with rapidly declining kidney function [100]. There are insufficient data to support the use of primary prophylactic anticoagulation in patients with NS and the decision to pre-emptively anticoagulate a patient should be made on a case-by-case basis. In 2014, a risk calculator based on the Markov decision model was published to calculate the risk vs. benefits for prophylactic anticoagulation for patients with primary membranous nephropathy [101]. Once a patient has developed a thrombotic event, anticoagulation should be continued until the resolution of the NS, since the risk of recurrence is extremely high. There are few case reports of using direct oral anticoagulants for treatment of thrombosis when warfarin is contraindicated, but there is no consensus or evidence for their use at this time.

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Renal Replacement Therapy in Acute Kidney Injury

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Introduction

Acute kidney injury (AKI) remains a common condition in hospitalized patients, especially amongst the critically ill in the intensive care unit (ICU), affecting approximately 50–60% of ICU patients [1], and it is an independent risk factor for mortality [2–7]. Unfortunately, the strategies to prevent AKI, aside from prerenal azotemia, contrast-associated AKI, and pigment-induced AKI, remain limited. Recently, several trials have suggested that a renal-protective strategy based on results of urinary biomarkers may be able to prevent AKI and mitigate AKI risk in some clinical situations [8, 9]. However, there remain no effective pharmacologic interventions for the treatment of most forms of intrinsic AKI. As a result, renal replacement therapy (RRT) remains the cornerstone of care in patients with severe AKI and the use of RRT for dialysis-dependent AKI (AKI-D) continues to increase steadily [1, 10]. Over the past three decades there has been a proliferation of modalities of RRT available for the management of AKI to now include intermittent hemodialysis (IHD), acute peritoneal dialysis (PD), continuous renal replacement therapy (CRRT), and "hybrid" therapies (prolonged-intermittent renal replacement therapy [PIRRT]). Despite the increasing technological sophistication of RRT, key management issues, such as the optimal timing of initiation, selection of modality, and dosing of RRT, remain controversial, and the clinical complexity and heterogeneity of patients with severe AKI has made clinical trials addressing these questions challenging.

This chapter focuses on key issues surrounding the use of RRT in the treatment of AKI, summarizing the indications for RRT initiation, the current evidence basis for the optimal timing of initiation of treatment, the selection of modality and dose of RRT, and RRT circuit considerations to optimize RRT circuit performance and function. Unfortunately, this chapter will not be able to address many other important factors to consider when delivering RRT for AKI such as medication dosing and nutrition support in RRT, transitions between therapies and when to stop acute RRT, or modality-specific RRT prescription details. Fortunately, there are many other resources and studies available that address these issues [11–17].

Renal Replacement Therapies in AKI

RRT is at first a misnomer, suggesting that its role is to *replace* kidney function when glomerular filtration rate (or creatinine clearance) has essentially ceased. Rather, RRT should instead be considered a supportive therapy (i.e. renal support therapy) in situations where the metabolic and fluid demands exceed native kidney function [18, 19]. In addition to fluid removal and clearance of waste products, RRT may also limit the negative, distant effects of AKI on nonrenal organs, including respiratory and cardiac dysfunction. Recent advances have made the provision of RRT easier and safer, but it is important to acknowledge that RRT only replaces excretory function (solute clearance and fluid removal) but does not provide or replace any of the myriad other kidney functions (i.e. tubular resorption of electrolytes and nutrients, endocrine regulation, or metabolic functions). Finally, clinicians must recognize that patients with AKI are distinctly different from those with end-stage renal disease (ESRD). The sudden, rapid decline

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of kidney function in AKI and multiorgan failure does not permit the body's adaptive responses seen in those with progressive chronic kidney disease.

Modalities

RRT utilizes an extracorporeal circuit containing an artificial membrane (hemodialysis [HD] or hemofiltration) or the patient's own peritoneal membrane (peritoneal dialysis) (see Table 13.1). Hemodialysis refers to the removal of solute and water across a semipermeable membrane by establishing and maintaining a concentration gradient between the blood flowing through the filter and the countercurrent flow of an electrolyte containing dialysate solution across the other side of the membrane (principle of diffusion) [21]. In hemofiltration, water and dissolved solutes are transferred across a semipermeable membrane by means of a transmembrane pressure gradient (principle of convection) [21]. Hemodiafiltration incorporates the removal of solute and water across a semipermeable membrane by both a concentration and transmembrane pressure gradient (diffusion and convection) [21]. PD uses the patient's peritoneum as a membrane across which fluids, electrolytes, and small molecules are exchanged by diffusion.

Further characterization of RRT is based on the duration. As such, there are continuous and intermittent forms of RRT. CRRT includes continuous veno-venous hemofiltration (CVVH), continuous veno-venous hemodialysis (CVVHD), continuous veno-venous hemodiafiltration (CVVHDF), and PD; intermittent techniques include IHD and newer "hybrid" therapies, such PIRRT, which has also been called sustained low-efficiency dialysis (SLED) (Figure 13.1).

Choice of Modality

In clinical practice, the choice of modality depends on the characteristics of the patient, availability of machines, and expertise of the clinical team [20]. Intermittent modalities are generally associated with greater fluctuations in metabolic and fluid status and an increased risk of intradialytic hemodynamic compromise (i.e. hypotension) whereas CRRT provides more sustained fluid removal and solute clearance, and is associated with less fluctuation (Figure 13.1 and Table 13.1). As such, CRRT is recommended for patients who do not tolerate fluctuations in fluid status or shifts in osmotically active molecules such as those patients with hemodynamic instability or acute brain injury [20]. The potential drawbacks of CRRT include greater restriction of mobility, continuous exposure to the extracorporeal circuit, need for anticoagulation, often unrecognized losses of amino acids, vitamins, and micronutrients, alterations in drug pharmacokinetics (PK), and dialysis-induced hypothermia to name a few (Table 13.1).

Intermittent RRT is usually preferred in patients who are hemodynamically more stable and able to tolerate greater fluctuations in fluid and metabolic status. IHD also provides greater minute-to-minute small solute clearance, which makes it far more effective in situations where life-threatening issues require emergent correction such as severe hyperkalemia with marked conduction abnormalities (i.e. complete heart block), acute poisonings, or profound metabolic acidemia. Intermittent RRT also allows more active physical therapy and rehabilitation by providing time off from therapy.

Hybrid therapies are variations of RRT that are usually provided daily for 6–18 hours. They offer some advantages of both intermittent and CRRT, and are often employed during the transition period from CRRT to intermittent RRT. There are multiple terminologies in the literature for hybrid therapies, with the most common being SLED and PIRRT [22].

Acute PD requires the insertion of a peritoneal dialysis catheter. It has theoretical advantages in that hemodynamic disturbances are rare and anticoagulation is not required. PD provides continuous clearance, but fluid removal rate and degree of solute clearance cannot be controlled as tightly as with IHD or CRRT. In addition, the risks of respiratory compromise from increased intra-abdominal pressure, pleural-peritoneal leak and intra-abdominal infection make it generally less suitable in the acute setting in adults, however acute PD remains a commonly used option in neonates and resource-limited settings. In patients with abdominal pathology, PD is usually contraindicated.

CRRT can be delivered as CVVH, CVVHD, or CVVHDF. Historically, diffusion, the clearance mode in hemodialysis, favors the removal of solutes with a lower molecular weight (MW) whereas convection (which underlies the process of hemofiltration) is more efficient at removing both low- and higher MW substances as it permits the transfer of molecules that can be accommodated by the size of the membrane pore. Indeed, there is some evidence that clearance of vancomycin (with MW approximately 1500 Da) can be improved with hemofiltration [23]. There is debate about whether there is a clinical benefit afforded by hemofiltration in the setting of AKI [24]. The potential benefit of removing a wider spectrum of solutes that are too large to be removed by hemodialysis (for instance inflammatory cytokines), would make hemofiltration an attractive therapy for certain types of AKI, for instance sepsis-associated AKI. However, small studies demonstrate that this difference in middle- or large-molecule clearance is low with modern high-flux membranes [25, 26]. Additionally, as

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Table 13.1 Characteristics of different RRT modalities used in AKI.

	Modality			
Parameter	**IHD**	**Hybrid RRT SLED/EDD/PIRRT**	**CRRT**	**PD**
Duration (h)	4–6	6–16	24	24
Frequency	Daily/alternate days	Daily/alternate days	Daily	Daily
Solute transport	Diffusion	Diffusion or convection or both	Diffusion or convection or both	Diffusion
Blood flow (ml/min)	200–350	100–300	100–250	NA
Dialysate flow (ml/min)	300–800	200–300	0–50	25–40
Urea clearance (ml/min)	150–180	90–140	20–45	15–35
Access	Central venous dialysis catheter	Central venous dialysis catheter	Central venous dialysis catheter	Peritoneal dialysis catheter
Need for anticoagulation	Usually but not absolutely necessary	Usually but not absolutely necessary	Yes	No
Fluctuations of osmotically active metabolites	++	+	Less; can occur in case of treatment interruptions	No
Fluctuations of fluid status	++	+	Less; can occur in case of treatment interruptions	No
Effect on ICP in patients with acute brain injury	Increase	Potential increase	Usually no change	No change
Effect on serum concentrations of renally cleared drugs	Major fluctuations	Some fluctuations	Less fluctuations	Less fluctuations
Infection risk	Line infection/bacteremia	Line infection/bacteremia	Line infection/bacteremia	Exit site infection; tunnel infection; peritonitis
Loss of nutrients into dialysate/filtrate	Yes	Yes	Yes	Yes

ICP, intracerebral pressure; RRT, renal replacement therapy; SLED, slow extended dialysis; EDD, extended daily dialysis; PIRRT, prolonged intermittent renal replacement therapy.
Source: Adapted from Bagshaw et al. [20].

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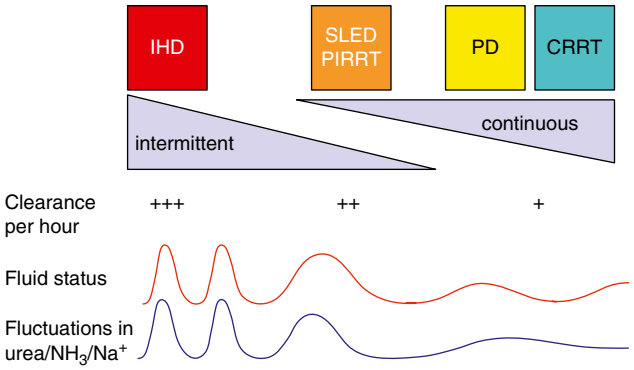

Figure 13.1 Renal Replacement Therapy Modalities in Acute Kidney Injury.

would be expected based on increased filtration fractions, CRRT circuit survival times are generally lower with higher rates of convection (CVVH) [23, 27]. Thus, any difference in minute-to-minute middle- and large-molecule clearance may be negated with less cumulative time on CRRT with higher rates of convection. This effect may be mitigated by CVVHDF combining both diffusion and convection, but there is no clinical data that this mode is superior. Indeed, a meta-analysis comparing hemofiltration and hemodialysis for AKI did not demonstrate any reliable differences in patient survival or kidney recovery [28].

It is commonly believed that CRRT is superior to IHD in critically ill patients but clinical trials have failed to confirm this [20, 29–37]. The propensity for seriously ill and more hemodynamically tenuous patients to receive CRRT rather than IHD, along with the inherent limitations of nonrandomized study designs, confounded many of the early observational studies that compared continuous and intermittent therapies. There are at least seven randomized controlled trials (RCTs) comparing CRRT and IHD (Table 13.2) [29–35]. In a multicenter RCT of 166 patients with AKI, Mehta et al. observed hospital mortality rates of 65.5% in patients randomized to CRRT, compared to 47.6% in patients randomized to IHD ($P < 0.02$) [29]. However, imbalanced randomization resulted in patients in the CRRT arm having greater severity of illness and a higher rate of liver failure, both of which were independently associated with increased mortality. After covariate adjustment, the investigators found no difference in mortality attributable to modality of RRT. Interpretation of this study is confounded further by a high rate of crossover between treatment modalities in both study arms. In a single-center RCT involving 80 patients, Augustine et al. reported more effective fluid removal and greater hemodynamic stability associated with CVVHD compared to IHD, but there was no difference in survival [31]. Similarly, Uehlinger et al. observed no difference in survival in 70 patients randomized to CVVHDF compared to 55 patients assigned to IHD [32].

The Hemodiafe study was a multicenter RCT conducted in 21 ICUs in France which demonstrated no difference in mortality in 184 patients randomized to IHD compared to 175 patients randomized to CVVHDF [33]. This study is particularly notable for the fact that IHD was delivered to

Table 13.2 Randomized controlled trials comparing modalities of RRT.

Randomized controlled trial	Number of CRRT patients	Mortality of CRRT group (%)	Number of control patients	Mortality of control group (%)	Unadjusted odds of death in control group (95% CI)
CRRT versus IHD					
Mehta et al. [29]	84	66	82	48	0.63 (0.3–1.4)
John et al. [30]	10	70	20	70	1.0 (0.1–6.6)
Augustine et al. [31]	40	68	40	70	1.12 (0.4–3.2)
Uehlinger et al. [32]	70	47	55	51	1.16 (0.5–2.5)
Vinsonneau et al. [33]	175	67	184	68	1.05 (0.6–1.7)
Lins et al. [34]	172	58.1	144	62.5	NA
Schefold et al. [35]	122	45.4	128	52.4	1.32 (0.80–2.19)
CRRT versus PD					
Phu et al. [38]	34	15	36	47	5.1
CRRT versus SLED					
Abe et al. [39]	30	37	30	17	NA

RRT, renal replacement therapy; CRRT, continuous renal replacement therapy; IHD, intermittent hemodialysis; PD, peritoneal dialysis; SLED, sustained low-efficiency dialysis; CI, confidence interval; NA, not available.

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patients despite marked hemodynamic instability, with little crossover between treatment groups. However, in the Hemodiafe study, IHD delivery was tailored to minimize risk of hemodynamic compromise – specifically, initial blood flow was limited to 250 ml/min, dialysate flow to 500 ml/min (both limiting speed of small solute clearance), dialysate sodium concentration was increased to 150 mEq/l (high dialysate sodium concentration is known to minimize risk of intradialytic hypotension), and dialysate temperature was decreased to 35.0°C to increase peripheral vascular resistance and vascular refilling. Mean IHD treatment duration was 5.2 hours and mean net fluid removal during each IHD session was only 2.2 l [33]. In the United States and many other countries, such optimized, tailored, and gentle IHD treatment is less common and challenging to deliver in those with AKI-D, making it difficult to extrapolate these results to daily practice.

The single-center CONVINT (Contininous versus intermittent renal replacement therapy Trial) trial was a prospective RCT comparing daily IHD with CVVH in 252 critically ill patients [35]. Survival rates at 14 days after RRT were 39.5% (IHD) versus 43.9% (CVVH) ($P = 0.50$). All-cause hospital and 30-day mortality rates were not different between the two groups (all $P > 0.5$). No differences were observed in days on RRT, vasopressor days, days on ventilator, or length of stay in hospital [35].

The propensity for hemodynamic instability and intradialytic hypotension during IHD has led to the suggestion that CRRT may be associated with an increased likelihood for recovery of renal function [40–42]. However, multiple meta-analyses comparing outcomes between these modalities of RRT have not found any convincing differences in any relevant patient-centered outcomes [36, 37, 43–46]. One meta-analysis included both randomized and nonrandomized studies and concluded that weaknesses in the quality of the studies significantly limited meaningful comparisons between modalities [43]. Based on weighting of the studies using an a priori assessment of study quality and comparability of severity of illness between treatment arms, the authors suggested that CRRT might be associated with a lower relative mortality risk. Subsequent meta-analyses differed in their criteria for including studies, resulting in minor differences in the calculated odds ratios (ORs) for mortality, but there were no differences in mortality associated with use of IHD or CRRT [36, 37, 44, 45]. The most recent systematic review including 21 RCTs and prospective cohort studies also concluded that RRT modality was not associated with in-hospital mortality or dialysis dependence [46].

Studies comparing other types of RRT are limited. In a small trial of 39 patients randomized to either CVVH or 12-hour PIRRT, cardiovascular tolerability and urea clearances were equivalent but less heparin was needed and acidosis was corrected faster in patients treated with PIRRT [47]. In another RCT in 60 patients comparing CVVHDF to 6–8 hours of PIRRT, there was no difference in ICU or 30-day mortality, but survivors in the PIRRT group had higher renal recovery rates and a shorter length of stay in ICU [39]. Finally, a systematic review and meta-analysis including seven RCTs and 10 observational studies concluded that PIRRT was associated with similar outcomes to CRRT [48].

There is a limited number of studies comparing PD to CRRT in adults. Two studies reported better results with CRRT but the clearance delivered by PD was low [49, 50]. One RCT found that CVVH was superior to PD in infection-associated AKI but the predominance of malaria as the cause of AKI limits the study's generalizability [38].

In summary, an understanding of the benefits and drawbacks of the different types of RRT is essential. Current data do not show superiority of any specific modality of renal support in patients with AKI. Rather than viewing these modalities as competing, we recommend viewing them as complementary therapies. Modality selection for an individual patient requires a consideration of the clinical characteristics of patients, the goals of RRT on a given day, provider expertise, and locally available technology and staffing resources. Importantly, guidelines do endorse the use of CRRT in those with (or at risk for) increased intracranial pressure as data does indicate that IHD causes a greater increase in intracerebral pressure (ICP) during the session compared to CRRT [51, 52]. Finally, as complimentary therapies, the choice of modality may need to be adjusted during the course of critical illness as a given patient's clinical status and renal support needs evolve.

Indications for Acute Renal Replacement Therapy

RRT for AKI (AKI-D) is initiated in approximately 15–20% of all critically ill patients [1]. The incidence of AKI-D in noncritically ill hospitalized patients is less well established and is widely variable across hospital settings and populations. Acute RRT for symptomatic hyperkalemia (or other severe electrolyte disorders), severe acidemia, symptomatic uremia, marked fluid overload leading to severe hypoxic acute respiratory failure, and toxic ingestions remain classic indications. However, there is wide divergence between providers about the severity of a given derangement (i.e. degree of hyperkalemia, blood urea nitrogen [BUN], pH, or fluid overload) that prompts dialysis initiation [53].

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The Kidney Disease Improving Global Outcomes (KDIGO) AKI guidelines [54] recommend that acute RRT should be initiated for "life threatening changes in fluid, electrolyte, and acid-base balance exist." However, it is important to note that KDIGO does not define what these specific life-threatening levels are. The KDIGO guidelines go on to state that the clinician should "consider the *broader clinical context, the presence of conditions that can be modified with RRT, and trends of laboratory tests* – rather than single BUN and creatinine thresholds alone – when making the decision to start RRT" [54]. This puts the onus back on the clinician teams to determine indications for acute RRT initiation in an individualized, patient-centered, goal-driven approach.

Renal support therapy in AKI has several goals: (i) return to and maintain fluid, electrolyte, acid-base, and solute homeostasis; (ii) to prevent complications of uremia; and (iii) to allow other supportive measures (such as antimicrobial or other drug therapy and nutrition support) to proceed without limitations in vulnerably acutely ill patients. However, acute RRT is not without risk and inherent complications – most having to do with RRT access (vascular or peritoneal) complications (infections and traumatic) and circuit-related factors such as need for anticoagulation, circuit-associated blood loss requiring transfusions, circuit failures limiting effective RRT delivery, and extracorporeal removal of medications such antibiotics (resulting in inadequate dosing) and nutrients. Therefore, initiating RRT must weigh the possible (or desired) benefits of therapy against the risks.

Timing of Dialysis Initiation

Decisions surrounding whether and when to initiate acute RRT continue to be amongst the most challenging and vexing issues in the hospitalized and/or critically ill patient over the last 60 years [1, 18, 19, 53–55], particularly in patients in whom imminent life-threatening complications are present.

In-hospital mortality amongst patients with AKI-D remains an all-too-frequent outcome afflicting 40–60% of patients [1, 37]. In a retrospective analysis of more than 10 000 ICU patients with AKI, Liborio et al. demonstrated that the excess hospital mortality at all stages and severities of AKI seems driven by the complications associated with AKI (hyperkalemia, metabolic acidosis, and >5% fluid overload) rather than AKI itself [56]. In theory, timely initiation of RRT might prevent the development of AKI complications, thereby possibly improving outcomes.

Timing of Dialysis: Definition

Throughout the literature, *conventional/delayed/late dialysis* initiation is defined as starting dialysis in an individual with advanced AKI (according to serum creatinine or urine-based criteria) when the patient reaches a predefined "life-threatening" indication for dialysis – symptomatic azotemia, hyperkalemia, severe acidemia, volume overload, and worsening hypoxia. Conversely, *early/preemptive dialysis* has had a wide range of definitions in different studies: lower serum BUN levels, earlier stages of AKI, and shorter time to initiation of dialysis. This has introduced a significant heterogeneity in the literature as to how this *early/preemptive* initiation has been applied. Finally, almost all trials comparing timing of dialysis have been performed in the ICU setting, presumably where the mortality impacts of a certain strategy may have the biggest effect.

Conventional/Delayed/Late RRT

In patients with AKI, it remains difficult to predict the trajectory for renal function and AKI recovery. Traditional tools such as BUN, creatinine, and urine output trends are helpful but have limitations. Some with advanced AKI will recover renal function quickly enough to never to require acute RRT. As mentioned above, acute RRT also carries risks including mechanical or infectious complications from the dialysis vascular access catheter, bleeding, loss of essential substances (e.g. nutrients, drugs), and increased cost, to name a few.

Isolated azotemia is rarely the only complication of AKI in hospitalized patients; encouragingly, studies evaluating the timing of initiation based purely on a BUN level (high or low) have shown no benefit to starting dialysis earlier [19, 55, 57]. This suggests that in those cases with isolated azotemia, a more deliberate, delayed approach to dialysis is likely safe.

More recently, the approach to studying RRT timing has centered on AKI staging according to criteria from the Acute Kidney Injury Network (AKIN) and KDIGO. The two largest trials to date were the Artificial Kidney Initiation in Kidney Injury (AKIKI) trial published in 2016 [58] and the Initiation of Dialysis Early Versus Delayed in the Intensive Care Unit (IDEAL-ICU) trial published in 2018 [59].

Both of these were multicenter trials enrolling critically ill patients exclusively in ICUs in France [58, 59]. They had opposite hypotheses (no benefit of early RRT initiation for AKIKI and benefit of early RRT initiation for IDEAL-ICU) and enrolled adult patients with AKI who did not have specific objective criteria for RRT initiation only if/when

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they developed KDIGO stage 3 AKI based on creatinine or urine output criteria [58, 59]. AKIKI did require that subjects have a clinical diagnosis of acute tubular necrosis (ATN), while IDEAL-ICU did not [58, 59]. Furthermore, both trials required patients to be critically ill – IDEAL-ICU requiring septic shock (i.e. on vasopressors) and AKIKI requiring shock on vasopressors and/or invasive mechanical ventilation [58, 59]. Both randomized patients who had stage 3 AKI to early versus delayed dialysis with those in the early group starting dialysis within 6 hours (AKIKI) or 12 hours (IDEAL-ICU) of reaching stage 3 AKI [58, 59]. Those in the late groups started RRT when they developed either a prespecified end point (i.e. hyperkalemia, severe acidemia, progressive fluid overload, or advancing hypoxemia) or if patients remained oligo-anuric without signs of renal recovery at 48 (IDEAL-ICU) [59] or 72 hours (AKIKI) [58].

AKIKI enrolled 619 patients and found no difference in the primary outcome of death at 60 days (48.5% in the early group vs. 49.7% in the delayed group, $P = 0.79$) [58]. Furthermore, although while almost all patients in the early group received dialysis, only 50% of patients in the delayed group required initiation of dialysis [58]. IDEAL-ICU enrolled 488 patients but was stopped after the second interim analysis based on the assessment of the safety board that it was futile to continue the study because completion of enrollment was unlikely to change the results of the trial significantly [59]. In the final analyses of the IDEAL-ICU study, 90-day mortality was 58% in the early group and 54% in the delayed group ($P = 0.38$) [59]. Similar to the AKIKI study, not all subjects in the IDEAL-ICU trial received RRT, with 97% in the early group receiving RRT while only 62% in the delayed group got RRT [59]. Of the remaining 38% of the delayed group who did not start RRT, 75% recovered renal function without requiring RRT (70 of the total 242 patients in the delayed group) [59].

In both trials, AKIKI and IDEAL ICU, mortality was lowest in those patients who were randomized to delayed RRT but never received it due to recovery of renal function, and mortality was highest in patients who were randomized to delayed RRT and actually started RRT. For clinicians managing patients with AKI, this constitutes a major challenge because at any point in time it is difficult to predict whether renal function will recover in the following 48 hours or not. While these two trials found no evidence of a survival benefit associated with earlier initiation of RRT, they also identify a need for better risk-stratification tools to differentiate between patients whose renal function will recover spontaneously, so that RRT can be avoided, and patients who will have progressive AKI, so that RRT can be timely started before the onset of fluid overload and serious metabolic derangements.

Limitations of both the AKIKI and IDEAL-ICU trial designs should be noted. Both trials excluded patients in whom there were objective criteria for earlier initiation of renal support, such as severe volume overload, hyperkalemia, and metabolic acidosis. While some have criticized both trials for significant use of intermittent RRT, it should be noted that utilization was equivalent in both treatment arms, that this represented usual care in the health systems where the trials were conducted, and that prior trials, such as the Hemodiafe trial [33], demonstrated no improvement in mortality associated with CRRT. The studies also did not address the question of whether a strategy of even earlier initiation of therapy would provide a survival benefit.

Early/Preemptive RRT: Theoretical Rationale

As Liborio et al. [56] demonstrated, hyperkalemia, acidemia, and fluid overload remain the primary life-threatening complications of AKI. Thus, it has long been postulated that dialysis initiation prior to development of life-threatening AKI complications may improve ICU and AKI outcomes. Over the last 10 years, while imperfect, data have emerged that add fuel to this debate: namely, is survival improved when early or preemptive RRT is started in an effort to prevent the development of emergent, immediately life-threatening indications for dialysis? Earlier RRT initiation may allow for prevention of fluid overload or improved fluid management, minimizing risk of hyperkalemia, and/or improved acid-base and azotemia control [18, 60]. Mitigating and minimizing these AKI complications may have an important impact on nonrenal organ function such as improved pulmonary function, faster liberation from mechanical ventilation, and improved vascular and cardiac function.

It is widely accepted in the critical care literature that fluid overload portends poor ICU prognosis and associates with organ dysfunction and impairment of organ and patient recovery through a variety of putative mechanisms. This association is independent of kidney functional status and more pronounced in patients with AKI, where fluid overload is consistently associated with mortality and lower renal recovery rates [61–64]. Studies by Bouchard et al. [63] and Vaara et al. [64] demonstrated that the presence of fluid overload at the time of acute RRT initiation for AKI doubles the risk of death. Additionally, both studies showed a dose-response relationship whereby a higher percentage of fluid overload led to progressive increase risk of death [63, 64]. When defining early versus delayed acute RRT on the basis of time from ICU admission to RRT initiation (within 2 or >2 days from ICU admission), in a retrospective review of the SOAP (Sepsis Occurrence in Acutely Ill Patients Study) study, Payen et al. showed improved survival in the early

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RRT initiation group and that the delayed group had higher cumulative fluid balance at the time of RRT initiation [65]. In patients with AKI due to ATN requiring acute RRT, a higher degree of fluid overload at RRT initiation was associated with worse kidney recovery (RRT-dependence) at 1 year [61]. Similary, Woodward et al. showed that in critically ill patients with AKI requiring CRRT, fluid overload >10% at the time of CRRT initiation was independently associated with major adverse kidney events (composite of mortality, RRT-dependence or inability to recover 50% of baseline eGFR (estimated glomerular filtration rate) if not on RRT) evaluated up to 90 days after discharge [66]. However, it should be recognized that while these observational data are hypothesis-generating, there have been no randomized trials demonstrating that early initiation of RRT to optimize fluid overload decreases mortality or promotes organ recovery.

Early Acute RRT Initiation

Prior meta-analyses including RCTs, prospective observational trials, and retrospective trials have suggested an improved survival with earlier initiation of dialysis [67, 68]. Following these meta-analyses and published nearly simultaneously with the AKIKI trial in 2016, Zarbock et al. in the Effect of Early vs Delayed Initiation of Renal Replacement Therapy on Mortality in Critically Ill Patients With Acute Kidney Injury [ELAIN] trial [69] performed a single-center RCT comparing preemptive versus conventional dialysis initiation for AKI in ICU patients. There are some important trial design differences between ELAIN, AKIKI, and IDEAL-ICU that warrant discussion. Most importantly, the inclusion criteria for ELAIN began with patients who had developed KDIGO stage 2 AKI with evidence of ATN despite optimal fluid resuscitation [69]. Participants were required to have ongoing catecholamine infusion requirements at time of enrollment, severe sepsis, refractory fluid overload, or a nonrenal Sequential Organ Failure Assessment (SOFA) score of 2 or higher [69]. This difference in AKI stage at enrollment (stage 2 in ELAIN and stage 3 in AKIKI/IDEAL-ICU) suggests that patients in ELAIN may indeed have received "preemptive" dialysis in the early RRT group. Additionally, the study mandated that all patients receive CRRT at the time of RRT initiation with clear, established guidelines to guide transition to intermittent modes of RRT or for discontinuation of dialysis. Finally, nearly all patients in both arms actually received dialysis.

In ELAIN, subjects were randomized to the early RRT group (starting within 8 hours of reaching stage 2 AKI and enrollment) or the delayed RRT group (starting within 12 hours of stage 3 AKI or an absolute indication [BUN >100 mg/dl, potassium >6 mEq/l, magnesium >8 mEq/l, severe oliguria, or diuretic-resistant organ edema]) [69]. As a single-center study, the total number enrolled was lower than either AKIKI or IDEAL-ICU, with ELAIN enrolling 231 subjects, 112 in the early group and 119 in the delayed group [69]. The primary outcome was 90-day mortality, which was 39.3% in the early group and 54.7% in the delayed group ($P = 0.03$), with a hazard ratio for death of 0.66 (95% confidence interval [CI] 0.45–0.97) for the early group [69]. However, in ELAIN, the median time difference from meeting full eligibility criteria to RRT initiation was only 21 hours (95% CI 18–24 hours) [69]. At a minimum, this begs the question as to whether a 15% absolute risk reduction for death in the early RRT arm of the study can realistically be plausible with such a short time difference between early versus late RRT initiation strategy.

Timing of Dialysis Initiation: Trial Limitations

As illustrated above, there are important limitations in many of the trials performed to date. Additionally, almost all trials have used some version of a creatinine- or urea-based definition of AKI as an inclusion criterion for the study. Given that fluid balance, acidemia, or electrolyte disturbances often drive decision-making and that azotemia is rarely the sole criterion for RRT initiation in the ICU, enrolling patients into clinical trials regarding the timing of RRT solely on the basis of meeting urea- or creatinine-based AKI definitions excludes patients from consideration who do not meet these AKI definitions yet still have indications for RRT such as diuretic-resistant fluid overload. No RCTs to date have evaluated RRT initiation on the basis of fluid balance or diuretic responsiveness alone.

Second, significant heterogeneity exists in study design and definitions of early versus late RRT: what is "early" in one trial may be "late" in another. For example, the early dialysis group in AKIKI [58] and IDEAL-ICU [59] and the late group in ELAIN [69] were determined by the same criterion: stage 3 AKI without complications.

Third, the mode of RRT at initiation varies widely between trials and even within some trials. While the RRT options are varied between studies, the choice of RRT modalities is generally balanced between early and late groups within a given trial in most circumstances. However, relative rates of use of intermittent and continuous therapies as initial RRT modalities should be considered in evaluating the applicability of trial results to individual practice settings where modality utilization may differ.

The largest multicenter, multinational trial, entitled Standard vs. Accelerated Initiation of RRT in Acute Kidney

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Injury (STAART-AKI), is still enrolling but does bear some of these same study design limitations. However, in general, the inclusion criteria for STAART-AKI starts with stage 2 AKI, requires equipoise by the healthcare team in regards to RRT need, and does not mandate initiation of RRT solely by stage 3 AKI criteria.

Timing of Dialysis: Summary

Unfortunately, data remain inconclusive to clearly guide clinical decisions at the bedside. Recognizing this limitation, the KDIGO AKI criteria suggest that clinicians should "consider the broader clinical context, the presence of conditions that can be modified with RRT, and the trends of laboratory tests. . . when making a decision to start RRT" [54]. However, one should keep in mind that these guidelines predate the publication of AKIKI, ELAIN, and IDEAL-ICU trials. While KDIGO AKI guideline review and revisions are ongoing, it would seem that these more recent studies do not argue substantially to change from the recommendation to "consider the broader clinical context of the individual patient" when weighing whether or not to timely initiate acute RRT.

In 2017, Feng et al. published a meta-analysis of nine RCTs on the timing of dialysis, which included the AKIKI trial but not IDEAL-ICU, that found no statistical difference between trials [70]. More recently, Pasin et al. reported a metanalysis including ELAIN, AKIKI, and IDEAL-ICU that concluded that early initiation of RRT in critically ill patients with AKI does not provide a clinically relevant advantage when compared with late RRT initiation [71]. Importantly, this study also points out the heterogeneity in the "early" and "late" initiation of RRT definitions and the need for specific studies in special populations such as sepsis or post cardiac surgery as well as the examination of performance and quality metrics of different RRT modalities in future interventional studies.

The Acute Dialysis Quality Initiative (ADQI) recommends a similar, individualized approach to RRT initiation whereby the demands on renal function and renal capacity are weighed with RRT initiated when significant discordance is seen between renal capacity/capability and demands on kidney function [18]. Critically ill patients have high "renal demands," frequently with significant burdens attributable to disease-related acidemia, fluid management, small solutes and electrolytes, and medication and toxin clearance. However, admittedly it remains difficult to determine which patients may benefit from early application of RRT versus a more patient, deliberate strategy with close observation [72]. Additionally, it remains challenging to predict which patients will need acute RRT and which are destined recover renal function without dialysis. Chawla et al. showed that failure to respond to a formal furosemide stress test (FST) predicted stage 3 AKI and the need for acute RRT (area under the receiver operating characteristic curve, 0.87 and 0.86, respectively) [73]. In a pilot trial that randomized FST nonresponders to early versus conventional RRT initiation, Lumlertgul et al. demonstrated that in ICU patients with AKI, those who responded to the FST had a very low rate of acute RRT needs (only 6/44 responders required RRT) [74]. Renal biomarkers may prove useful to predict RRT needs. Urine tissue inhibitor of metalloproteinase 2 and insulin-like growth factor-binding protein 7 (TIMP-2*IGFBP-7) can risk-stratify those at high risk for progression to severe forms of AKI, with higher values (>2.0) strongly associated with development of stage 3 AKI [75–77]. Research is needed to determine if TIMP-2*IGFBP-7 results or trends over time can discriminate patients who will and will not require RRT, as well as hard outcomes such as death or RRT-dependence.

Dose of Renal Replacement Therapy in AKI

The goal of RRT for AKI management is to optimize solute control and fluid balance according to the specific needs of the patient. It is important to recognize that the dose of RRT is a dynamic metric that should be individualized according to the clinical context of the patient, but should also adhere to best evidence-based practice once the patient achieves a steady-state of solute and volume control.

Intermittent Hemodialysis Dose in AKI

There are limited data regarding the "adequate" per treatment dose of IHD in AKI. Paganini et al. retrospectively evaluated mortality in relation to the delivered dose of HD in critically ill patients with AKI [78]. Among patients at either the low or high spectrum of severity of illness, HD dose had no impact on patient outcome. However, in patients with an intermediate severity of illness score, the delivery of HD dose in excess of the 50th percentile (Kt/V approximately 1) was associated with lower mortality risk than the delivery of lower doses of HD [78]. While these data are consistent with evidence relating dose of IHD to outcomes in patients with end-stage kidney disease receiving maintenance hemodialysis, it should be recognized that these observational data cannot differentiate between the dose of HD per se and patient-specific factors that limited the delivered dose of therapy as the mediator of the increased mortality associated with the lower delivered dose of HD.

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In a study evaluating the effect of treatment frequency of IHD on outcomes among patients with AKI, Schiffl et al. alternately assigned 160 critically ill patients with ATN to daily or alternate-day IHD and found that patients who received daily IHD had both lower mortality 14 days after discontinuation of RRT (28% vs. 46%, $P = 0.01$) and shorter duration of AKI (9 ± 2 vs. 16 ± 6 days, $P = 0.001$) [79]. However, it is important to note that the dose of IHD delivered to the alternate-day treatment group was low (mean delivered Kt/V_{urea} 0.94 ± 0.11). This resulted in a markedly elevated time-averaged BUN concentration, which may have been the reason that this group had a higher incidence of complications, including gastrointestinal bleeding, alterations in mental status, and sepsis [79]. In addition, the alternate-day IHD group had more episodes of intradialytic hypotension when compared to the daily IHD group: 25 ± 5 vs. 5 ± 2, respectively. Nonetheless, while this study demonstrated that increasing the delivered dose of IHD from a very low dose by increasing the frequency of treatment improves survival, one cannot conclude that increasing the frequency of a more "adequate" alternate-day or a thrice-weekly schedule to daily therapy would improve survival.

When examining data related to dose of IHD for AKI, it is important to recognize that several studies have established that there is a significant discrepancy between prescribed and successfully delivered dose, therefore more frequent monitoring of the delivered dose of IHD with pre- and post-BUN is recommended [79–81].

In summary, when evaluating the dose of IHD, both the dose per treatment (Kt/V_{urea}) and the treatment frequency need to be considered. Special considerations in critically ill patients with AKI should be noted, such as different urea generation rates and urea volume of distribution due to volume overload. The KDIGO consensus guidelines recommend a delivered Kt/V_{urea} of 3.9 per week when using IHD for the management of AKI [54]. However, this recommendation is based on the arithmetic sum of a Kt/V_{urea} of 1.3 per individual HD treatment (assuming three HD sessions per week and supported by the average weekly Kt/V_{urea} dose delivered in the less-intensive arm of the ATN trial [82]) but not on urea kinetic modeling [83]. Therefore, a more precise recommendation is that in the absence of specific medical indications (e.g. severe hyperkalemia, acute drug intoxications, volume overload, etc.) in patients with AKI, there is no additional benefit to providing HD more frequently than every other day, with a delivered single-pool Kt/V_{urea} of >1.2 per treatment (urea-reduction ratio [URR] >0.67) [84].

CRRT Dose for AKI

In the case of CRRT, the total effluent rate (ml/kg/h) is used to determine the dose according to the different modalities of CRRT (Table 13.3). There is no consensus in relation to which patient's weight to use (admission weight, ideal weight, or current weight) but we tend to use current weight to account for the acute changes in volume of distribution from fluid expansion (during critical illness and resuscitation for shock) and systemic inflammation.

There are more data regarding the appropriate dosing of CRRT in the literature (Table 13.4). Early work by Ronco et al. randomized 435 patients to one of three CVVH doses, defined by ultrafiltration rates of 20, 35, and 45 ml/kg/h [2]. Mortality was markedly lower in the intermediate- and high-dose arms (43% and 42%, respectively) compared to the low-dose arm (59%, $P < 0.001$). The absence of a survival benefit of high-dose therapy compared to the intermediate dose argued against a linear relationship between dose and outcome. However, it is also possible that a survival benefit from high-dose CRRT was blunted by a competing mortality that was CRRT-dose dependent (i.e. inadequate antimicrobial drug dosing). Similarly, Saudan et al. reported an overall improved mortality when dialysate (CVVHDF) was added to a fixed dose of CVVH thereby increasing the total CRRT dose [86]. In this study, a total of 102 patients were randomized to receive CVVH with a mean ultrafiltration rate of 25 ± 5 ml/kg/h, and 104 patients were randomized to CVVHDF with a mean ultrafiltration rate of 24 ± 6 ml/kg/h and a mean dialysate flow rate of 18 ± 5 ml/kg/h. The addition of diffusive clearance was associated with an increase in 28-day survival from 39% to 59% ($P = 0.03$) and increased 90-day survival from 34% to 59% ($P = 0.0005$). In contrast, Bouman et al. did not observe improvement in mortality with higher doses of CRRT (20 vs. 48 ml/kg/h) [85]. However, the overall study mortality of less than 30% suggests that the enrolled patients were not fully representative of most critically ill patients with AKI requiring RRT. Finally, Tolwani et al. reported no difference in outcomes in 200 patients randomized to

Table 13.3 Total effluent dose according to the different modalities of CRRT.

CRRT modality	Total effluent dose (ml/h)
CVVH or CVVHF	Pre-filter replacement fluid rate (ml/h) + post-filter replacement fluid rate (ml/h) + fluid removal rate (ml/h)
CVVHD	Dialysate rate (ml/h) + fluid removal rate (ml/h)
CVVHDF	Pre-filter replacement fluid rate (ml/h) + post-filter replacement fluid rate (ml/h) + fluid removal rate (ml/h) + dialysate rate (ml/h)

CVVH or CVVHF, continuous veno-venous hemofiltration; CVVHD, continuous veno-venous hemodialysis; CVVHDF, continuous veno-venous hemodiafiltration.

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Table 13.4 Interventional studies examining higher vs. standard intensity dose of RRT.

Study	Participants	Interventions	Population	Mortality	AKI recovery
Ronco [2]	425	CVVH 20 vs. 35 vs. 45 ml/kg/h	75% post surgical, 12% septic	59% vs. 43% vs. 42% ($P < 0.002$)	
Bouman [85]	106	CRRT 20 vs. 48 ml/kg/h	58% post cardiac surgery, 100% respiratory failure, 100% inotrope or pressors	31.2% vs. 25.7% (P = ns)	No difference
Saudan [86]	206	CVVHF 25 ml/kg/h vs. CVVHDF 42 ml/kg/h	60% septic	61% vs. 41% ($P = 0.03$)	
Tolwani [87]	200	CVVHDF 20 vs. 35 ml/kg/h	54% septic, 77.5% respiratory failure	44% vs. 51% (P = ns)	
Palevsky (ATN) [82]	1124	CVVHDF 20 vs. 35 ml/kg/h IHD 3/wk HD vs. 6/wk HD	63% septic, 80.6% respiratory failure	51.5% vs. 53.6% ($P = 0.47$)	No difference
Bellomo (RENAL) [88]	1508	CVVHDF 25 vs. 40 ml/kg/h	49.4% septic, 73.9% respiratory failure	44.7% vs. 44.7% ($P = 0.99$)	No difference
Joannes-Boyau [89]	140	SVHF 35 vs. HVHF 70 ml/kg/h	100% septic, 97% respiratory failure	59.2% vs. 62.1% ($P = 0.94$)	No difference
Combes [90]	224	HVHF 80 ml/kg/h + CVVHDF vs. SOC with CVVHDF if needed	Post cardiac surgery with severe shock	36% vs. 36% (P = ns)	No difference

CVVH or CVVHF, continuous veno-venous hemofiltration; CVVHDF, continuous veno-venous hemodiafiltration; HVHF, high-volume hemofiltration; IHD, intermittent hemodialysis; SOC, standard of care; SVHF, standard-volume hemofiltration. P = ns, nonsignificant.

CVVHDF at 20 vs. 35 ml/kg/h of total effluent dose [87]. Survival to ICU discharge or 30 days, whichever was earlier, was 49% in the patients randomized to the higher dose group, compared to 56% of patients randomized to the lower dose group.

Subsequently, two large multicenter studies evaluated dosing of RRT in AKI: the VA/NIH Acute Renal Failure Trial Network (ATN) study [82] and the Randomized Evaluation of Normal versus Augmented Level (RENAL) Replacement Therapy study [88]. The ATN study utilized a strategy that included both HD in hemodynamically stable patients and either CVVHDF or SLED/PIRRT in hemodynamically unstable patients [82]. In the intensive management strategy, HD and SLED/PIRRT were provided daily (except Sunday), and CVVHDF was provided with a total effluent dose of 35 ml/kg/h; in the less-intensive strategy, HD and SLED/PIRRT were provided every other day (except Sunday), and CVVHDF was dosed at 20 ml/kg/h. In both treatment arms, the target delivered single-pool Kt/V_{urea} for HD and SLED/PIRRT was 1.2–1.4 per treatment, with an actual delivered dose during HD of 1.32 ± 0.36. Sixty-day all-cause mortality was 53.6% in the 563 patients randomized to intensive therapy, compared to 51.5% in the 561 patients randomized to the less-intensive therapy (OR 1.09, 95% CI 0.86–1.40, $P = 0.47$). There was also no difference in the duration of RRT, recovery of kidney function, or the course of nonrenal organ failure [82].

The RENAL study randomized 1508 critically ill patients with AKI to a higher intensity CVVHDF ($n = 721$, total effluent dose of 40 ml/kg/h) vs. a lower intensity CVVHDF ($n = 743$, total effluent dose of 25 ml/kg/h) without an option for IHD/PIRRT as initial RRT modality [88]. There was no difference in the primary end-point of 90-day mortality (44.7% in each group, $P = 0.99$). In addition, no differences in 28-day mortality, RRT-dependence, total days of RRT, or nonrenal organ failure were found [88]. A post hoc study of extended follow-up (median of 43.9 months) did not reveal a difference in mortality or RRT-dependence between these two intensity strategies of CRRT dosing [91].

Joannes-Boyau et al. conducted a multicenter randomized trial including 137 critically ill patients with septic shock and AKI to evaluate even higher doses of continuous hemofiltration [89]. The study tested standard-volume hemofiltration (SVHF, $n = 71$, 35 ml/kg/h) vs. high-volume hemofiltration (HVHF, $n = 66$, 70 ml/kg/h) for a 96-hour period based on the hypothesis that HVHF may improve hemodynamics and mortality in critically ill septic patients

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by improving removal of sepsis-related pro-inflammatory cytokines, but the results showed no difference in the primary end-point of 28-day mortality (SVHF 59.2% vs. HVHF 62.1%, $P = 0.94$). There was also no difference in secondary outcomes that included 60-day and 90-day mortality, duration of mechanical ventilation, duration of RRT, kidney recovery, and length of hospital stay [89]. A subsequent metanalysis by Clark et al., including four randomized trials, concluded that insufficient evidence exists of a therapeutic benefit for routine use of HVHF for critically ill septic patients with AKI [92]. In a more recent study, Combes et al. conducted a multicenter randomized trial including patients with post-cardiac surgery severe shock to test early HVHF ($n = 112$, 80 ml/kg/h × 48 hours, followed by standard-dose CVVHDF until resolution of shock and recovery of kidney function) vs. standard of care with delayed CVVHDF only for persistent/severe AKI ($n = 112$) [90]. Again, there was no difference in 30-day mortality between groups (36% for both groups). There was also no difference in the secondary outcomes of 60-day and 90-day mortality, ventilator-free days, kidney recovery, and length of hospitalization [90]. However, it is important to note that 43% of the subjects in the standard of care arm did not receive any RRT. In addition, patients in the HVHF arm had more frequent hypophosphatemia, metabolic alkalosis, and thrombocytopenia [90].

In summary, although some small single-center studies have suggested that increased intensity of RRT is associated with improved outcomes, this approach is not supported by data generated from large multicenter studies. Differences between study results most likely reflect differences among study designs (delivered RRT dose, timing of RRT initiation, etc.) and study populations (acuity of critical illness, presence of sepsis, etc.). Wang et al. conducted a meta-analysis of seven randomized clinical trials addressing higher versus standard intensity dose of RRT and concluded that higher intensity RRT does not affect mortality outcomes [93]. However, the authors highlighted that more participants assigned to higher intensity RRT remained dependent on RRT at 28 days (29.7% for the higher intensity group vs. 24.9% for the standard intensity group, relative risk of 1.15, 95% CI 1.00–1.33, $P = 0.05$) [93]. Nonetheless, one should note that kidney recovery (RRT-dependence) was a secondary outcome in all the interventional studies included in this meta-analysis and there may be ascertainment bias of the outcome as higher intensity RRT lowers solute burden and thus possibly reduces solute-driven urine output, which is one of the cornerstone metrics of kidney recovery examination.

As seen with IHD, there is usually a discrepancy between prescribed versus true delivered CRRT dose due to CRRT down time (circuit failures, CRRT therapy fluid bag changes, and procedures, imagining studies or surgery that require temporarily stopping CRRT). Based on the research in CRRT dose, for most critically ill AKI patients, an effective delivered dose 20–25 ml/kg/h is recommended [11, 54, 94]. However, to account for this CRRT down time, it is reasonable to prescribe 25–30 ml/kg/h of total effluent dose for CRRT. Finally, it is critical to recognize that the effluent dose of CRRT should be individualized according to the specific needs of the critically ill patient, who may benefit from higher intensity CRRT in specific scenarios such as severe metabolic acidosis, severe hyperkalemia, or severe hypercatabolic states that require higher intensity solute control. Therefore, it is fundamental to develop a systematic way of iterative assessment and adjustment of RRT goals according to the clinical status of the patient [95].

PIRRT/SLED Dose in AKI

Dosing of dialysis in PIRRT is less well established. It remains unclear which index is best to guide dose in PIRRT (URR, Kt/V_{urea}, effluent flow) [96]. As with IHD and CRRT, PIRRT therapy should be individualized to patients needs to accomplish the specified daily RRT goal (correction of hyperkalemia, acidemia control, fluid removal). Similarly, there are no data to support prolonged exposure to high-dose PIRRT. One option to determine a PIRRT prescription when transitioning from a CRRT device is to first decide on the effluent dose that one would use for that given patient on CRRT (i.e. 25 ml/kg/h, 35 ml/kg/h, etc.), then calculate the total daily effluent needs for the patient based on that CRRT dose (i.e. 30 ml/kg/h × 80 kg = 2400 ml/h × 24 h = 72 000 ml/day = 72 l/day). Finally, divide total effluent needs by the number of hours that PIRRT is planned to give hourly effluent flow rates on PIRRT (72 l/day/10 h = 7.2 l/h = 120 ml/min) [22]. If using a standard HD device, customizing the PIRRT prescription to achieve a Kt/V_{urea} of ~0.7–0.9 per treatment for a total of six treatments per week can provide a weekly Kt/V_{urea} of 3.0–3.5 based on urea kinetic modeling [83], which is above RRT dosing thresholds although data are still limited to provide more conclusive recommendations with the use of PIRRT.

It is important to remember that PIRRT will have widely variable impacts on drug dosing of dialyzable drugs, especially important for antimicrobial agents. Duration of PIRRT, flow rates in PIRRT, and fluid removal during PIRRT will all impact a given drug's pharmacokinetics (PK). There are expanding PK data for many antimicrobials during PIRRT; however, these data are generally based on small PK studies and require that PIRRT be operated under the exact operating characteristics that are described in the published research protocol.

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RRT Circuit Considerations

When prescribing and managing acute RRT in AKI, there are many factors beyond the RRT modality, timing of RRT initiation, and RRT dose to consider and that do often affect whether RRT application proves successful at achieving the specified daily goal. These circuit-based factors include dialysis vascular access, use of convective versus diffusive clearance, type of membrane, circuit anticoagulation (especially for CRRT), medication dosing, and many others. We will conclude by addressing some of these topics briefly.

Dialysis Vascular Access

Hemodialysis vascular access is of paramount importance when providing acute RRT for AKI. Insertion is often the rate-limiting step to RRT initiation and poorly functioning vascular access is often the foil of the acute RRT procedure. Given that a well-functioning vascular access is vital for RRT circuit function and, ultimately, being able to achieve the goal-based acute RRT, care must be taken to select the optimal site, appropriate catheter size and length, depth and angle of insertion. If the nephrologist is not the proceduralist for catheter insertion, at a minimum the providers should discuss and agree on these points prior to the procedure to improve the odds of a well-functioning access on initial insertion.

Data to guide catheter insertion remains limited. KDIGO recommends a nontunneled temporary dialysis catheter for RRT in AKI [54]. However, there are cases where AKI recovery is delayed in whom a tunneled longer-term dialysis catheter may be appropriate to lower the rate of catheter-related infection. Additionally, KDIGO recommends varying lengths of catheters depending on site of insertion (internal jugular [IJ] versus femoral) and preferred sites, but these guidelines are not based on evidence and, in our opinion, are inaccurate as the catheter length recommendations are too short and the guidelines eschew the left IJ site [54].

Morgan et al. [97] performed a randomized trial on IJ dialysis catheter length in AKI requiring CRRT comparing shorter versus longer catheters with the goal of achieving a catheter tip in the right atrium (RA) in the long catheter group and superior vena cava position (SVC) in the short group with the primary end-point being CRRT circuit life. Catheter lengths were determined by site and group, with the short catheter group getting 15 cm catheters placed in right IJ veins and 20 cm in left IJ veins (per KDIGO guidelines) and the long catheter group getting 20 cm catheters in right IJ veins and 24 cm in left IJ veins. Positioning of the tip in the RA was achieved in 81% of the longer catheter group and only 9% of the shorter catheter group. Mean CRRT circuit life was prolonged by 6.5 hours (24 vs 17.5 hours, $P = 0.001$) and dialysis delivery was more effective (91% of dialysis dose delivered vs 81%, I = 0.001) in the longer catheter group [97]. There were no differences in complication rates, including rates of atrial fibrillation. RA (or caval atrial junction) insertion is safe with current soft catheter materials and design and there is a very low rate of vascular or atrial erosions due to dialysis catheters [97]. Our and other centers' experience mirror the results of the Morgan study. As a result, we recommend use of catheters that are placed as far distally as possible, with a goal that the tip be at the caval atrial junction or in the right atrium when using the IJ insertion site. Catheters placed in the right IJ vein are preferred as they have a straighter intravascular course and are associated with fewer complications; however we differ from KDIGO in that we favor properly positioned left IJ vein catheters over catheters in the femoral veins.

The KDIGO preference of femoral over left IJ sites is based on older trials where left IJ catheters were unquestionably too short [54]. For example, the Cathedia study group found comparable small solute clearance and similar catheter and dialysis circuit function comparing IJ venous (primarily right) to femoral venous access [98]. However, this study did not specify catheter length or size and 100% of IJ catheters were less than 20 cm in length (usually 16 cm) and no comment was made regarding ultimate catheter tip position. This suggests that the performance of the IJ catheters may have been worse than had they used a longer catheter. Furthermore, in this study, 30% of catheters in the IJ group were placed on the left side, where they still used relatively short catheters (<20 cm), which likely contributed to worse left IJ catheter performance compared to the right IJ and femoral sites [98].

Finally, in a separate study, the Cathedia study group compared infection rates between IJ and femoral vascular access sites, demonstrating that catheter-related infection rates were similar between IJ and femoral sites [99]. However, prespecified subgroup analysis did suggest that infection rates were different in the group with the highest quartile body mass index (BMI) which was BMI > 28 kg/m^2 [99]. Thus, caution is warranted when selecting catheter site for those with BMI > 28 kg/m^2, which is common in US-based ICUs.

Dialyzer Membranes

In the modern era, all membranes used for acute RRT in AKI are high-permeability, high-flux, biocompatible membranes, especially for CRRT, where each device manufacturer generally has a limited selection of membranes.

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With IHD and PIRRT (and with some CRRT machines), the clinician is theoretically free to select from a wider array of membranes available in a given country. However, in practice, a given institution only carries a few options and these are almost always the standard high-flux, highly permeable, biocompatible, artificial, noncellulose based membranes. The typical membrane materials are polyacrylonitrile (AN69), polyarylethersulfone (PAES), and polyethersulfone (PES). There are no data suggesting that one type of membrane provides improved outcomes.

There are copious preclinical and human case series reported from outside of the Unites States on specialized membranes and adsorption devices for selective cytokine, endotoxin or other toxin removal, especially in sepsis, but these specialized membranes are generally not approved for use outside of research studies.

Dialysis Fluids/Solutions and Buffers

With all modes of RRT (IHD, PIRRT, CRRT) there is a wide variety of commercially available dialysis solutions for both dialysate and replacement fluids with varying electrolyte concentrations. Solutions (especially for CRRT) can alternatively be customized and compounded in a given hospital. However, there is a risk of compounding errors and bacterial contamination inherent with compounding large quantities of CRRT fluids [100]. As a result, we recommend the use of commercial solutions. Most commercially available solutions are primarily bicarbonate-buffered solutions, with near abandonment of lactate or acetate as the primary buffer over the last 20 years.

Anticoagulation Strategies

An important advantage of IHD and PIRRT is that the use of anticoagulation is usually not required. However, anticoagulation for CRRT circuit survival is strongly encouraged by KDIGO and we agree [54]. CRRT circuit survival with anticoagulation is improved when using heparin, regional citrate anticoagulation (RCA), direct thrombin inhibitors, and other strategies [101–107]. Systemic anticoagulation with heparin, low-molecular weight heparins, and direct thrombin inhibitors obviously carries risk of systemic bleeding. RCA is well proven in CRRT and has been shown to have superior circuit survival effects when compared to both heparin and no anticoagulation with no systemic bleeding risk and few complications that are easily prevented (i.e. systemic hypocalcemia) with attention to established protocols [101–107]. KDIGO endorses the use of RCA in CRRT for patients both with and without increased bleeding risks [54].

Summary

AKI requiring RRT is common and increasing among hospitalized patients, especially among patients with concomitant critical illness. Generally, prolonged therapies (CRRT and/or PIRRT) are preferred for the most vulnerable and critically ill patients. Care must be taken to individualize the timing of RRT initiation and the dose of RRT to accentuate the benefits of RRT while minimizing the potential harms such as anticoagulation, impacts on drug clearance (especially antimicrobial agents), and nutrition. Finally, we strongly encourage a multidisciplinary goal-driven approach to each day's RRT endeavors. The specific goals for RRT (CRRT, PIRRT, IHD, PD) should be reassessed each day and the RRT plan should be designed to best accomplish the targeted goals (rapid correction of severe hyperkalemia, tailored fluid removal, etc.). Accountability toward achieving the desired goals of therapy should be assured through multidisciplinary quality improvement programs [95]. RRT in patients with AKI continues to be associated with a high mortality rate, but an individualized, dynamic, and goal-driven renal support program could optimize patient outcomes.

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Part 3

Primary Diseases of the Kidney

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14

Renal Biopsy

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GRADE Recommendations

Introduction

The prevalence of kidney disease is rising, with chronic kidney disease (CKD) affecting more than 1 in 10 individuals in Australia, and acute kidney injury (AKI) complicating more than 130,000 hospital admissions each year [1]. Parenchymal renal diseases (glomerular, tubular, or vascular) are leading causes of both CKD and AKI (when pre- and postrenal causes have been excluded), and renal biopsy remains the gold standard method for their diagnosis, assessment of prognosis, and management. There have been many advances in renal biopsy techniques since its inception that have greatly enhanced the success and safety of this procedure. These have included modifications to patient positioning, introduction of real-time imaging guidance, and the use of automated biopsy needles. Performing a kidney biopsy has been shown to change the prebiopsy clinical diagnosis in 44% of cases and to change therapy in 30% of cases [2].

The procedure itself involves the removal of tissue from the renal cortex for histopathological examination by a specialist pathologist. The percutaneous approach is standard, and the procedure is typically guided by ultrasound and performed under local anesthesia, with the patient in the prone position. Both coaxial and noncoaxial needle techniques have been described. Renal biopsy has been found to be safe and efficacious, with an acceptably low risk of complications and with sufficient tissue being obtained in more than 95% of cases [3]. The most common complications are minor and major bleeding, both of which are usually self-limiting and rarely life-threatening. Several risk factors for complications have been identified, including uncontrolled hypertension, coagulopathy, advanced age, and reduced kidney function. The evidence behind Renal biopsy is seen in table 14.1.

Indications

Performing a renal biopsy is warranted if it is needed to diagnose or guide the treatment of a suspected disease which is associated with significant morbidity and/or mortality, if the natural history of the suspected disease can be improved with treatment, and if the treatment for the suspected disease is appropriate for and acceptable to the patient. Renal biopsy is useful to assess the chronicity and activity of a disease, while serial renal biopsy may be performed to assess the natural history or response to treatment. Although there are no defined criteria for performing a renal biopsy, there are many accepted indications:

- *Nephrotic syndrome* is the most frequent indication for renal biopsy. In this setting, biopsy provides information for the diagnosis, staging, and activity of disease [4].
- Persistent proteinuria >1 g per day or persistent proteinuria <1 g per day in the presence of haematuria or renal dysfunction are also common reasons to perform a renal biopsy. In the presence of haematuria, biopsy should only be undertaken after malignancy has been excluded.
- *Systemic diseases with suspected renal involvement* (e.g. systemic lupus erythematosus, multiple myeloma, amyloid) often necessitate renal biopsy to guide decisions surrounding prognosis and treatment.

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Table 14.1 Recommendations for renal biopsies.

Treatment	Recommendation	Certainty of evidence	Strength of recommendation
Education	We recommend that patients and their carers be provided with relevant information regarding the renal biopsy procedure, including why they are having one, and the pre- and post-biopsy complications. It should be provided with clarity and cover the topic in a way that is appropriate for their level of health literacy.	*Low or very low*	Weak [1, 2]
Pre-biopsy medication	We recommend that aspirin is continued in patients with high cardiovascular risk or ceased 3 (to reduce major bleeding) or 7 days prior (to reduce minor bleeding) in patients with low cardiovascular risk. In patients receiving anticoagulation, bridging anticoagulation is recommended in patients with mechanical valves and in those with a high thrombotic risk.	*High*	Strong [3]
	We suggest that desmopressin should be used sparingly and with caution.	*Low or very low*	
Positioning for renal biopsy	We recommend that native renal biopsies be performed in a prone position, that transplant renal biopsies be performed in a supine position, and that biopsies in patients who are obese or who have difficulty lying prone (pregnancy or respiratory difficulty) be performed in the in a supine anterolateral position.	*Moderate*	Weak [4, 5]
Imaging	We recommend that native renal biopsies be performed using real-time ultrasound guidance, with the use of computed tomography localization being used for difficult biopsies.	*Moderate (US guidance)* *Low (CT guidance)*	Weak [6]
Biopsy needles	We recommend the use of spring-loaded 16-gauge needles for native and transplant biopsies.	*Moderate*	Moderate [7]
Post-biopsy care	We recommend strict bed rest following a renal biopsy and a 6-h observation period in patients at low risk of bleeding. Patients at high risk of bleeding should be observed overnight.	*Moderate*	Moderate [8]
	Routine post-biopsy imaging or hemoglobin measurement is not recommended.	*Low (post biopsy tests)*	
Management of bleeding complications	We recommend the use or radiological (glue, gel or coiling) or surgical management to arrest persistent post-biopsy bleeding.	*Low*	Weak

GRADE assessment of the certainty of the evidence (9): High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different* is low. Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different* is moderate. Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different* is high. Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different* is very high. **Substantially different = a large enough difference that it might affect decision-making*.

- *Unexplained AKI* is an indication for renal biopsy, following exclusion of prerenal or postrenal disease. Glomerulonephritis, interstitial nephritis, and systemic diseases with renal involvement can all present with AKI.
- *Unexplained CKD* may prompt investigation with renal biopsy, although the diagnostic yield is typically low and the risk of bleeding complications is Higher than biopsy of a non disease kidney due to possible smaller and harder to biopsy kidneys. Biopsy in this setting can be useful in assessing the likelihood of disease recurrence following future kidney transplantation.
- *Transplant dysfunction* (impaired biochemical function, proteinuria or hematuria) is another indication for renal biopsy to assess for evidence of allograft rejection, drug toxicity, and recurrence of primary disease.

The decision of whether to proceed with renal biopsy in a diabetic patient can be particularly challenging. Diabetes has become the most common cause of CKD in the western world [5] and diabetic nephropathy can coexist with other causes of parenchymal renal disease. It is currently difficult to predict the degree of diabetic renal injury based on clinical or laboratory findings alone. New-onset nephrotic-range proteinuria or hematuria or a rapidly progressive decline in renal function are common indications for renal biopsy in this population. A recent meta-analysis [6] examining the predictors of nondiabetic kidney disease in 4876 patients across 48 studies

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(range from 3% to 82.9% incidence) found that higher systolic blood pressure, worse diabetes control (worse diabetic control), longer diabetes duration, and the presence of retinopathy reduced the positive predictive value of renal biopsy in diagnosing nondiabetic renal disease.

Contraindications

Absolute contraindications to percutaneous kidney biopsies include coagulopathy and uncontrolled hypertension (>160/100 mmHg). Additional relative contraindications include the presence of small kidneys, hydronephrosis, pyelonephritis, abnormal anatomy (e.g. polycystic kidney disease), a solitary kidney, technical difficulties (patients who are obese, unable to lie flat, or uncooperative), and the special circumstances of pregnancy, amyloid kidney, and the pediatric setting.

When a contraindication to percutaneous renal biopsy exists, alternative methods of obtaining renal tissue can be considered, including open, laparoscopic, and transjugular approaches. These differ in terms of their safety profile and sample adequacy. Open and laparoscopic biopsies are associated with a low risk of bleeding and excellent tissue adequacy, but require general anesthesia and longer recovery time. Sample adequacy is lower with transjugular renal biopsy and there is a risk of contrast-induced nephropathy. Although the reported complication rates of transjugular biopsies are similar to those seen in the percutaneous approach, the baseline risk of individuals clearly differs significantly such that direct comparison of complications rates between the approaches cannot be performed.

Epidemiology

Accurate estimation of the frequency of renal biopsies across the world is particularly challenging. The capacity of a country to perform kidney biopsies, and the number of kidney biopsies performed, will depend on their healthcare infrastructure and the availability of trained practitioners (nephrologists, radiologists, scientists, pathologists). The Global Kidney Health Atlas recently reported that pathological services for renal biopsy were routinely available for 23% of countries, but were rarely or never available in 24% and 14% of countries, respectively. In a recent systematic review of national biopsy registries, regional databases, and single-center cohorts, Fiorentino et al. [6] also found that there was significant variation in the rate of renal biopsies between countries, ranging from 10.8 per million population per year in Romania and Serbia to 215 per million population per year in the United States and Australia. Although hypothesis-generating, their analysis was potentially confounded by their consideration of different time periods (before year 2000 and after), reporting and coding bias, and heterogeneity of the indications for biopsy.

Procedure

Technique

Percutaneous renal biopsies are commonly performed under local anesthetic. Occasionally, in the pediatric setting or in anxious individuals, conscious sedation or general anesthesia is used, which requires the patient to be fasted and monitored closely during and after the procedure. Lignocaine (1% or 2%) is infiltrated from the skin to the renal capsule, and the biopsy needle is advanced along the anesthetized tract. The patient is asked to pause at full inspiration such that the lower pole of the kidney is in contact with the needle tip, and the triggering mechanism of the needle is then released. The lower pole of the left kidney is usually selected for biopsy because it tends to be more caudal and superficial than the right kidney, is away from the major vessels and organs, and is easiest for right-handed operators. Between one and three cores of tissue are sampled and the procedure time is generally between 15 and 30 minutes. No fewer than seven glomeruli and one artery are required for a sample to be considered adequate, while optimally 10 glomeruli and two arteries should be provided for analysis. Real-time evaluation for adequacy by a pathologist or scientist confirms adequate tissue while minimizing the number of passes.

Positioning

Although the percutaneous native renal biopsies were traditionally performed in an upright position, they are now routinely performed with the patient in the prone position, often with a pillow or sandbag under the umbilicus, which is used to splint the kidney. The lateral decubitus position is another possible approach, which has not been found to be different to prone positioning in terms of procedure time or risk of complications [7], but may be more comfortable for some patients, especially those who are unable to lie prone (e.g. during pregnancy). Transplant biopsies are routinely performed in the supine position; the supine anterolateral approach may be appropriate in obese patients. In the setting of kidney transplants, consideration should be given to whether the transplanted kidney is located in the intraperitoneal (e.g. simultaneous kidney pancreas transplant) or extraperitoneal space.

Imaging Guidance

Historically, renal biopsies were done blind or by palpation. However, with the widespread availability and ease of use of imaging techniques, ultrasound-guided renal biopsy has become the standard of care for native and transplant kidney biopsies. Ultrasound may be used for real-time

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guidance or for surface marking and approximating needle direction and depth. Computed tomography (CT)-guided renal biopsy may be considered preferable in obese patients, patients with complicated anatomy, and those with inadequate kidney imaging on ultrasound since it may offer better resolution and tissue contrast. The Caring for Australasians with Renal Impairment (CARI) guidelines [8] have recently summarized the evidence comparing imaging modalities, reporting that ultrasound guidance is superior to blinded renal biopsy with respect to the number of glomeruli, number of passes, and risk of bleeding complications, but there are insufficient data directly comparing CT and ultrasound guidance. Many of the published studies have been confounded by the use of different needle types and historical cohorts.

Needle Size

Although a number of needle sizes are available, the majority of renal biopsies are performed using 14-gauge (internal diameter 900–1000 μm), 16-gauge (internal diameter 600–700 μm), or 18-gauge (internal diameter 300–400 μm) needles. Both 14-gauge and 16-gauge needles are used in adults, while 18-gauge needles are generally reserved for the pediatric setting since the internal diameter of the needle is only marginally larger than an adult glomerulus (200–250 μm) [9, 10]. When selecting a needle size, bleeding risk and sample adequacy are the key considerations. The conclusion from the recently published CARI guidelines was that 16-gauge needles obtained more diagnostic tissue with the smallest number of passes (predominantly compared to 18-gauge needles) and with the smallest number of minor and major bleeding complications (predominantly compared to 14-gauge needles).

Sample Preparation

Preparation of the renal tissue for processing requires provision of clinical information to the scientist or pathologist and careful handling of the tissue. Normal saline should be used to wash the tissue from the needle. The samples are subsequently placed in the appropriate fixatives and transport media for light microscopy, immunofluorescence, and electron microscopy. If no anatomical pathology scientist is present, specimens may be placed in normal saline for transport (assuming sample examination will occur within a couple of hours). For samples being sent to a referral center, tissue can be divided and prepared prior to dispatch. Fresh tissue is required for immunofluorescence to preserve antigenic activity. A sample for electron microscopy should be placed in 3% glutaraldehyde, if available. The remainder of the tissue should be placed in formalin, for light microscopy only.

Practitioner

Although renal biopsy can be performed by a nephrologist, radiologist, or other practitioner, it is well accepted that experienced proceduralists have lower complication rates. In a survey of practitioners in Europe, renal biopsies were performed in 60% of centers by nephrologists, in 30% of centers by radiologists, and in 10% of centers by both [11]. In many countries, competency in performing renal biopsies is a compulsory component of nephrology training. Two-thirds of nephrology trainees in the United States have learned renal biopsy, but few perform it in their consultant practice. Both Australia and the United Kingdom have recommended that learning skills in renal biopsy be part of nephrology training. There is currently no formal accreditation process for nonproceduralists.

Preprocedure Care

Prebiopsy Evaluation

The prebiopsy evaluation is an essential component of the renal biopsy procedure and should include a detailed clinical history and examination in addition to targeted laboratory testing and imaging to evaluate the risk of bleeding. Relevant aspects of the clinical history relate to knowledge and previous experience of renal biopsy, mobility and ability to lie prone, psychological condition, and level of comprehension (e.g. anxiety, confusion, language barrier). Enquiring about the patient's current and recent medications, as well as previous bleeding difficulty following procedures (e.g. dental work) or a history of a bleeding disorder, is important to assess their risk of bleeding. In all cases, written informed consent must be obtained from the patient or their legally authorized representative prior to the procedure. This may necessitate the use of interpreters.

The recently published CARI guidelines [12] have highlighted the significant psychosocial impact of renal biopsy on patients and caregivers, and a qualitative study by the same group identified the need for better communication, education, and pre- and post-procedure psychological support. Similar studies in other percutaneous biopsies (including breast, cervical, liver, and prostate) have reported similar findings. All patients should receive psychological preparation prior to their procedure to ensure a patient-centered, holistic approach to care and to prevent the adverse physiological sequelae of anxiety, including hypertension, a heightened perception of pain, and a delay in recovery time. Ideally, patients should be provided with information regarding the procedure itself, the sensations

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the patient can expect to feel (e.g. sharpness, numbness), and the expected post-procedure recovery (e.g. mobilization, return to normal activities).

Investigations

Investigations should include a full blood count to quantify hemoglobin and platelet count, a coagulation profile to assess activated partial thromboplastin time and prothrombin time, and an ultrasound to diagnose anatomic abnormalities, including a solitary kidney, small or polycystic kidneys, hydronephrosis, and vascular abnormalities. Although abnormal coagulation should be corrected prior to biopsy, there is in sufficient evidence to inform the specific international normalized ratio (INR) and the platelet threshold at which proceeding with renal biopsy is safe. In most published studies, patients undergoing renal biopsy were required to have an INR below or equal to 1.5, and a platelet count greater than 50 000/μl. However, appropriate values should be individualized, taking into account other factors associated with the risk and consequences of bleeding, such as the use of antiplatelet and anticoagulant agents, and the presence of hypertension, uremia, complex anatomy, and anemia. Transfusion should be considered if serum hemoglobin is<80 g/l and is recommended if <70 g/l.

The use of bleeding time in assessing the risk of bleeding complications remains controversial. It is a poor predictor of the risk of surgical bleeding and its clinical benefit in the setting of percutaneous renal biopsy has not been studied. [13]. Although a correlation between bleeding time and "clinical" bleeding in patients with uremia has been reported, prior knowledge of bleeding time has not been shown to reduce bleeding complications in native or transplant biopsies in the limited available studies [14, 15].

Antiplatelet Agents

The use of antiplatelet medications is very common in the renal biopsy population. In many centers, these agents are routinely discontinued between 5 and 7 days prior to the procedure. However, in a patient with preexisting cardiovascular disease this approach increases the risk of a periprocedure cardiovascular event [16], and results in delayed diagnosis and treatment. Specifically, cessation of aspirin has been shown to increase the risk of stroke by three- to fourfold and to increase the relative risk of recurrent myocardial infarction by 40%, especially when performed soon after a myocardial infarct or percutaneous coronary intervention.

Although the continuation of aspirin has been associated with an increased risk of minor bleeding complications (e.g. hemoglobin drop ≥1.0 g/dl), it has not been associated with an increased risk of major bleeding events (e.g. need for transfusion, interventional, or surgical procedure). Therefore, the current recommendation is to continue aspirin in patients at high risk of cardiovascular events, including those with a history of coronary stent (particularly within 3 months of bare metal stent or 12 months of drug-eluting stent insertion), symptomatic myocardial ischemia or peripheral vascular disease (including patients with a peripheral stent), or previous ischemic stroke. In patients at low risk for a cardiovascular event, aspirin should be withheld for 3 or 7 days to prevent major and minor bleeding complications, respectively. There are limited data examining the safety of continuing clopidogrel at the time of biopsy, and most guidelines recommend that it should be withheld for 7 days prior. Aspirin and clopidogrel can be recommenced 24–48 hours after an uncomplicated procedure since most complications will have occurred within this time.

Anticoagulants

In patients who are taking oral anticoagulants there is a need to balance the bleeding risk against the thrombosis risk. Warfarin should be ceased 5 days prior to renal biopsy in all patients. Bridging anticoagulation should be used in all patients with a mechanical valve, antiphospholipid syndrome, high-risk thrombophilia, or venous thromboembolism within 3 months. The role of bridging anticoagulation is less clear in atrial fibrillation. In low-risk patients, interruption of warfarin without bridging anticoagulation appears to be noninferior to the use of bridging anticoagulation for the prevention of thromboembolism [17]. However, these results may not be generalizable to high-risk atrial fibrillation patients, in whom the decision should be individualized according to patient risk. For patients who receive bridging anticoagulation, low molecular weight heparin should be withheld for 24 hours, while unfractionated heparin should be ceased 4–6 hours prior to biopsy. Anticoagulation can be recommenced 24–48 hours following an uncomplicated procedure. For patients requiring hemodialysis, the biopsy should be performed at least 6 hours after treatment (if heparin is administered) and the use of intradialytic anticoagulation should be avoided the following day. It is important to note that there are no data on the effect of new oral anticoagulants on renal biopsy complication rates.

Desmopressin

A heightened risk of bleeding in the context of uremia is well described [18]. It is likely that many factors contribute to this bleeding propensity, including dysfunctional von Willebrand factor (vWF), platelet membrane abnormalities

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and impaired aggregation, anemia, and increased prostacyclin and nitric oxide levels. The use of procoagulants prior to biopsy (e.g. desmopressin acetate) has been suggested as a potential strategy to lessen minor and major bleeding. Desmopressin is a synthetic analog of antidiuretic hormone, which increases platelet adhesion to the blood vessel wall by augmenting plasma levels of factor VII and vWF. It has been shown to normalize bleeding time in uraemia for up to 4–8 hours (Vigano GL, Mannucci PM, Lattuada A, et al. Subcutaneous desmopressin (DDAVP) shortens the bleeding time in uremia. Am J Hematol. 1989;31(1):32–5.] from CARI) when delivered intravenously at a dose of 0.3 μg/kg over a period of 20–30 minutes.

Despite its use in many units, there is little evidence to support the clinical benefit of desmopressin. A single randomized controlled trial of 162 patients undergoing native renal biopsy compared the use of desmopressin to placebo, showing a 16.8% reduction in minor bleeding, but no difference in post-biopsy hemoglobin [19]. Of note, all patients in this study had preserved renal function and normal coagulation, so the generalizability of their findings is unclear. Moledina et al. conducted an observational study of 159 hospitalized adults who underwent native kidney biopsy in the United States to investigate acute kidney disease. After adjustment for blood urea nitrogen, desmopressin was associated with a lower risk of blood transfusion (odds ratio 0.24, 95% confidence interval [CI] 0.06–0.88). In contrast, a retrospective study of 22 renal biopsies in children showed no difference between desmopressin and placebo. The most serious adverse event of desmopressin (severe hyponatremia) is reported in 1 in 10 000 cases, but other symptoms, including hypotension, tachycardia, facial flushing, nausea, and abdominal pain, can also occur [20, 21].

Other treatments, including tranexamic acid, recombinant erythropoietin to achieve a hematocrit >30%, conjugated estrogens, and cryoprecipitate, have not been formally investigated in the setting of renal biopsy. The impact of dialysis on uremic bleeding is also unclear.

Bleeding Prediction Scores

Mejia-Vilet et al. recently developed a score to predict bleeding complications using a high-risk population of hospitalized patients undergoing renal biopsy in Mexico. They found that CKD features on ultrasound, blood urea nitrogen >50 mg/dl, haemoglobin <11 g/l, and platelet count <150/mm^3 were independent predicters of bleeding complications following renal biopsy. The discriminative power of their model was supported in a small, prospective validation cohort, but external validation has not been undertaken.

Post-procedure Care

The post-biopsy period is critical to detection of major complications of renal biopsy, including hemodynamic compromise, macroscopic haematuria, urinary tract obstruction, and severe loin pain. Although mild pain or discomfort is expected post biopsy, severe pain over the site may indicate bleeding. Based on the findings of early studies [22], patients were historically observed overnight following a renal biopsy. However, several advances in the renal biopsy technique have subsequently enhanced the safety of the procedure. The optimal timing of observation after biopsy in the modern day is debatable and should be guided by the likelihood of complications. In general, at least 4–8 hours of observation are recommended following an uncomplicated biopsy in a low-risk patient, but as many as one-third of complications may occur after 8 hours [14]. Almost all complications are detected by 24 hours [23]. For patients at high risk of complications, and for those who live remotely, overnight observation is often warranted.

During this observation time, vital signs are monitored frequently and every voided urine sample is examined for macroscopic hematuria. Unless contraindicated due to fluid restriction, a high fluid intake is encouraged to reduce the risk of clot formation in the urinary tract. Following discharge, patients should be instructed to seek medical attention in the setting of escalating pain, recurrence or worsening of hematuria, or inability to pass urine. Most published protocols also suggest a period of abstinence from intense physical labor, exercise or heavy lifting for 1–2 weeks after a biopsy, but there is no evidence to support this recommendation.

The utility of routine post-biopsy hemoglobin testing or imaging in predicting clinical complications has not been demonstrated. The presence and size of post-biopsy hematomas on routine imaging does not correlate with the development of clinically significant complications [24], although the absence of a hematoma has a high negative predictive value for bleeding. Routine haemoglobin testing and imaging following biopsy are therefore of limited utility in patients who are otherwise asymptomatic.

Complications

The most common complication after renal biopsy is bleeding, which may manifest as hematuria, perinephric hematoma, loin pain, hypotension, or a drop in hemoglobin. Most minor bleeding can be managed conservatively, but moderate bleeding, indicated by severe pain, large perinephric hematoma or hypotension, should be initially managed with

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blood transfusion. In the setting of severe bleeding, with hemodynamic instability and failure to respond to conservative measures, radiological intervention or surgical management is required to secure hemostasis.

Estimating the risk of bleeding complications after biopsy is made difficult by differences in how bleeding is defined and diagnosed between studies, by variation in patient selection, technique, and needle type, and by likely reporting bias. A recent meta-analysis of 118 064 biopsies (87 studies selected) showed complication rates included perinephric hematoma in 11% of the kidney biopsies, macroscopic haematuria in 3.5%, bleeding requiring blood transfusion in 1.6%, and interventions to stop bleeding in 0.3%. Death attributed to native kidney biopsy was rare, occurring in only an estimated 0.06% of all biopsies [25]. Complication rates were higher in hospitalized patients and those with AKI. Recent further reassurance that outpatient biopsy is safe when a low-risk patient group is selected can be seen in a large single-center uncontrolled study of the outcomes of 824 outpatient kidney biopsies (448 native and 326 transplant kidney) with both a minor or major complication identified in 11.4% of patients within 4–6 hours post biopsy [26]. An older meta-analysis of almost 10 000 biopsies [27] reported that macroscopic hematuria occurred in 3.5% (95% CI 0.3–14.5%) of patients, while 0.9% (95% CI 0.4–1.5%) of patients received a blood transfusion and only 0.6% (0.4–0.8%) required angiography. The incidence of perinephric hematoma is likely to be much higher than other reported complications. Based on studies performing CT-guided biopsies in a historical cohort, as many as 91% of patients have evidence of a hematoma on imaging [28].

In the older meta-analysis, the study-level predictors of bleeding complications included the use of 14-gauge needles (compared with 16-gauge and 18-gauge), higher serum creatinine (>2.0 mg/dl), AKI in >10% of cases, a baseline hemoglobin <12 g/dl, a mean age >40 years, and systolic blood pressure >130 mmHg [27]. The safe blood pressure threshold to prevent bleeding is debatable, with most studies and guidelines recommending a maximum acceptable systolic blood pressure of 140 or 160 mmHg.

Other rare complications include arteriovenous fistula formation (0.1–0.5%), infection, pneumothorax, and injury to adjacent organs, including the liver, spleen, pancreas, and colon. Nephrectomy is required after <0.1% of cases and the risk of death is similarly low.

Transplant Biopsies

There are many single-center studies in the literature addressing the safety of transplant biopsy in the contemporary setting of spring-loaded needles and ultrasound localization and guidance. The reported rates of complications tend to be lower than in native biopsy: hematoma in 1%, major and minor bleeding in 2–3%, hemoglobin decline in <1%, and graft loss in <0.04% [29, 30].

Monoclonal Gammopathies and Paraprotein Disease

It has been suggested in historical cohorts that patients with monoclonal gammopathies and paraprotein diseases are at increased bleeding risk (Colm C. Magee Nephrology Dialysis Transplantation, Volume 21, Issue 12, December 2006, Pages 3601–3602, https://doi.org/10.1093/ndt/gfl578). However, large cohort studies have not supported this, except in reporting a higher risk of hemoglobin decrease >1 g/dl [31–33].

Pregnancy

In the setting of pregnancy, the risk of biopsy must be weighed against any potential benefit of diagnosis and treatment, especially considering that treatment options may be limited due to teratogenicity. Renal blood flow is increased in pregnancy, which may increase complication rates, and modification of biopsy technique may be necessary (e.g. patient positioning). A recent systematic review of 39 studies (mostly retrospective case series) of renal biopsies performed during pregnancy or in the perinatal period [34] found that the complication rate was 7% during pregnancy, compared to only 1% after delivery. All major complications occurred during gestational weeks 23–28. Studies in which biopsy was performed for suspected glomerulonephritis or preeclampsia reported that therapy was altered in 66% of cases. Bleeding Complications after Pediatric Kidney Biopsy- A systematic Review and Meta-analysis .Charles D. Varnell, Hillarey K. Stone and Jeffrey A. Welge Clinical Journal of the American Society of NephrologyJanuary 2019, 14 (1) 57-65; DOI: https://doi.org/10.2215/CJN.05890518.

Pediatrics

Renal biopsy in the pediatric setting has the added difficulty of small kidneys and variable patient cooperation. A recently published systematic review of 23 studies including 5504 renal biopsies reported that between 11% and 18% of pediatric patients develop a hemotoma after biopsy, but only 0.9% require a blood transfusion. As few as 0.7% of biopsies resulted in an additional intervention due to post-biopsy complications. Meta-regression suggested that the use of real-time ultrasound guidance did not modify the risk of hematoma or requirement for blood transfusion or further intervention. In general, pediatric biopsies are performed

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with a spring-loaded device and 18-gauge needle [35]. The number of passes should be ≤3 in 80% of cases. There does not appear to be a difference in the rate of complications between inpatient and outpatient procedures.

Conclusion

Renal parenchymal biopsy remains an invaluable diagnostic and prognostic tool for nephrologists, providing key information that can be used in conjunction with biochemical and urinary testing. In modern-day practice with automated, spring-loaded needles and ultrasound guidance, it has very low complication rates and high diagnostic yield, altering patient management in many cases. Developing a patient-centred approach to renal biopsy, with appropriate education and support, will be the next step to further improving the safety and acceptability of the procedure.

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15

Minimal Change Disease and Focal Segmental Glomerulosclerosis in Adults

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Introduction

Minimal change disease (MCD) and focal segmental glomerulosclerosis (FSGS) are the two key forms of idiopathic nephrotic syndrome (INS). In 1999, evidence-based recommendations for treating adult INS were published in *Kidney International* [1]. In 2012, the Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for Glomerulonephritis published its first guideline on glomerular diseases [2]. A review of the literature shows that our current clinical and pathogenic knowledge of MCD and FSGS has evolved. Increasing studies report that in addition to idiopathic cases, MCD and FSGS could be caused by multiple factors, such as virus infection, allergies, Hodgkin disease, and medications. As such, MCD and FSGS denote histologic findings, rather than two single diseases. Patients with genetic mutations affecting podocyte biology, including slit diaphragm structure, actin cytoskeleton of podocytes, and foot process structure, may develop their first episode of nephrosis as an adult when it does not respond to immunosuppressive treatment. This indicates that some patients with mutations and who fail immunosuppression may explain some of the variability in observed treatment effects in trials. Although corticosteroids and calcineurin inhibitors (CNIs) are still the cornerstone treatments, new insights into pathogenesis and novel treatment options have been developed, targeting the pathogenic process with more efficacy and fewer adverse effects. For example, rituximab (RTX), a monoclonal antibody targeting B cells, is an efficient and safe alternative. A number of new agents targeting pathogenic factors, such as CD80, have now been tried in the treatment of MCD and FSGS (Table 15.1, Table 15.2).

This chapter examines the evidence for management of MCD and FSGS in adults.

Definition

MCD

The definition of MCD has not changed. It presents as nephrotic syndrome of sudden onset. In adults proteinuria is less selective than in children. Hypertension may be present. A functional impaired glomerular filtration rate is common at onset and normalizes with remission. Light microscopy and immunofluorescence show normal glomeruli. Electron microscopy discloses diffuse foot process flattening and no immune deposits.

FSGS

The onset of nephrotic syndrome can be more insidious than in MCD, except in the so-called glomerular tip lesion, a variant whose response to treatment is comparable to that of MCD [3–5]. In other forms, an explosive onset also seems to entail a response to treatment closer to MCD than in more progressive forms, although considerable overlap exists [6]. Hypertension and renal insufficiency are not unusual from the onset. Proteinuria is not selective. A detailed discussion of the histopathology of FSGS is beyond the scope of this chapter but is available elsewhere [7–9]; it is not covered further here because there are no implications for specific treatment [7].

Remission

Complete Remission

There is general agreement regarding the definition of complete remission (CR): 24 hours proteinuria of ≤0.3 g, with serum albumin of ≥3.5 g/dl and stable renal function.

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Table 15.1 Treatment of adult minimal change disease (MCD).

Treatment	Recommendation	Certainty of evidence	Strength of recommendation
Prednisone/ prednisolone	We recommend that corticosteroids be given for initial treatment of nephrotic syndrome. We suggest prednisone or prednisolone be given at a daily single dose of 1 mg/kg (maximum 80 mg) or alternate-day single dose of 2 mg/kg (maximum 120 mg). The initial high dose of corticosteroids should be maintained for a minimum period of 4 weeks if complete remission is achieved, and for a maximum period of 16 weeks if complete remission is not achieved. In patients who remit, we suggest that corticosteroids be tapered slowly over a total period of up to 6 months after achieving remission. For infrequent relapses, we suggest using the same initial dose and duration of corticosteroids.	Low	Strong (use of corticosteroids) Weak (dose and duration)
Calcineurin inhibitors (CNIs)	For patients with relative contraindications or intolerance to high-dose corticosteroids, we suggest short-term intravenous methylprednisolone (0.8 mg/kg/day for 10 days) + tacrolimus monotherapy (0.05 mg/kg/day for 16–20 weeks) subsequently tapering over approximately 18 weeks. We suggest oral CNIs for relapsed patients despite cyclophosphamide, or patients of childbearing age. Cyclosporine initiates at 3–5 mg/kg/day or tacrolimus 0.05–0.1 mg/kg/day in two equally divided doses. Following 3 months of stable remission, tapered to reach the minimum dose that maintains remission, for 1–2 years.	*Low*	Weak
Cyclophosphamide	We suggest oral cyclophosphamide 2–2.5 mg/kg/day at a single dose as tolerated for 8 weeks for patients with frequently relapsing MCD and with relative contraindications or intolerance to high-dose corticosteroids.	*Low*	Weak
Mycophenolate mofetil	We suggest oral mycophenolate mofetil for patients intolerant to corticosteroids, cyclophosphamide, and/or CNIs. 500–1000 mg twice daily for 1–2 years.	*Low*	Weak
Rituximab	We suggest using rituximab for patients with frequently relapsing or corticosteroid-resistant MCD.	*Low*	Weak

GRADE assessment of the certainty of the evidence: High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different* is low. Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different* is moderate. Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different* is high. Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different* is very high. *Substantially different = a large enough difference that it might affect decision-making.

Partial Remission

Partial remission (PR) has been variably defined among publications. An acceptable definition is 24 hours proteinuria of >0.3 and <3 g and/or a decrease of at least 50% from the baseline level, along with a rise of serum albumin of ≥3 g/dl and stable renal function.

Relapse

The definition of relapse also varies among publications. In general it is defined by recurrence of massive proteinuria (24 hours proteinuria of >3.5 g). Frequent relapse (FR) is generally defined as more than two relapses observed over the last 6 months or more than four relapses observed over any 12-month interval.

Steroid Dependent

Steroid dependent (SD) usually referrers to two consecutive relapses during corticosteroid therapy, or within 14 days of ceasing therapy.

Epidemiology

Clinically, FSGS and MCD share numerous similarities, but show different onset age, treatment responses, and prognosis (Table 15.3). MCD is the most common cause of INS, accounting for 70–90% in children under 10 years old and 10–25% in the adult population with an increase in percentage of FSGS [10]. In addition to age, ethnicity is an important predictor of the percentage of nephrotic patients

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Table 15.2 Treatment of adult focal segmental glomerulosclerosis (FSGS).

Treatment	Recommendation	Certainty of evidence	Strength of recommendation
Prednisone/ prednisolone	We recommend that corticosteroids be given for initial treatment of nephrotic syndrome. We suggest prednisone or prednisolone be given at a daily single dose of 1 mg/kg/day (maximum 80 mg) or alternate-day single dose of 2 mg/kg (maximum 120 mg). The initial high dose of corticosteroids should be maintained for a minimum period of 4 weeks if complete remission is achieved and for a maximum period of 16 weeks if complete remission is not achieved. In patients who remit, we suggest that corticosteroids be tapered slowly over a total period of up to 6 months after achieving remission.	*Low*	Strong (use of corticosteroids) Weak (dose and treatment duration)
Calcineurin inhibitors	We suggest oral cyclosporine for steroid-resistant patients. Cyclosporine initiates at 3–5 mg/kg/day in two equally divided doses. Following 4–6 months of stable remission, tapered to reach the minimum doge that maintains remission, for 1–2 years.	Moderate	Weak
Mycophenolate mofetil	We suggest oral mycophenolate mofetil + high-dose dexamethasone for patients with steroid-resistant FSGS intolerant to cyclosporine.	*Low*	Weak

GRADE assessment of the certainty of the evidence: High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different* is low. Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different* is moderate. Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different* is high. Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different* is very high. *Substantially different = a large enough difference that it might affect decision-making.

Table 15.3 Clinical features of minimal change disease (MCD) and focal segmental glomerulosclerosis (FSGS).

	MCD	FSGS
Age prevalence	● 70–90% in children <10 years old ● 10–25% in adults	● No
Male/female ratio	● 2 : 1 in children ● 1 : 1 in adults	● 1 : 1
Secondary forms	● Rare	● Frequent
Familial aggregation	● Rare	● Frequent
Light microscope	● Almost normal	● Focal and segmental sclerosis
Immunofluorescence	● IgM± ● C3±	● IgM± ● C3± ● IgA± ● IgG±
Electron microscope	● Diffuse foot process effacement	● Diffuse foot process effacement
Treatment resistance	● Rare	● Frequent
Frequent relapse	● Frequent	● Rare
Progression to end stage renal disease	● Rare	● Frequent

C3, complement 3; IgA, immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M. Renal deposition of C3, IgA, IgG and I gM were semi-quantified using immunofluorescence staining, grading as 0 (lack of deposits), 1 + (trace), 2 + (weak), 3 + (moderate), and 4 + (strong).

with MCD. The percentage of nephrotic patients with MCD is highest in Asian and Caucasian populations, while the percentage of nephrotic patients with underlying FSGS is highest in African-American populations. FSGS is the most common form of glomerular histology in North American (19.1%), the second most common in Europe (14.9%) and Latin America (15.8%), and the fifth-most common in Asia (6.9%) [11, 12]. In recent years, the incidence and the prevalence of nephrotic FSGS have steadily risen [13, 14].

Genetic predisposition is proposed in patients with FSGS because of their familial aggregation and the geographic variation in prevalence. Patients of black African ancestry are twice as likely to develop FSGS than patients of white

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European origin [18]. This is true of most histological variants, especially the cellular variants [19, 20]. The exception is the glomerular tip lesion [3, 4]. The response to corticosteroid treatment in black people is distinctly worse than in white people [21], although the overall outcome of the disease in each race follows the same trend. In recent years, familial cases with MCD have also been described [22], suggesting a possible genetic origin of the disease. MCD and FSGS are characterized by diffuse foot process effacement. As the intricacies of podocyte cell biology have been unraveled, increasing causative genes regulating slit diaphragm structure (nephrin, NPHS2, CD2AP) and actin cytoskeleton of podocytes (MYO1E, myocin IIA, α-actinin-4) have been identified [23–26]. The role of high-risk APOL1 genotypes in the development of glomerulosclerosis is still under investigation. Genetic testing for pediatric nephrotic syndrome and adult FSGS is controversial, and it can be considered for patients with congenital and infantile forms of nephrotic syndrome (children <1 year of age) or less than the two forms but with steroids resistant nephrotic syndrome (SRNS), nephrotic syndrome associated with other syndromic features, or familial forms of SRNS/FSGS [27]. Genetic FSGS is typically resistant to corticosteroids. The value of routine implementation of genetic testing in adults remains to be resolved in the future [28–30].

Pathophysiology

MCD and FSGS are both examples of pathogenic mechanisms that primarily affect the podocyte (podocytopathies). They are not characterized by immune deposits, but there may be a role for circulating factors in the pathogenesis of both diseases. In recurrent FSGS following kidney transplantation, early renal biopsy shows widespread foot process effacement on electron microscopy, hallmarks of MCD, while repeated biopsy suggests evolution to an FSGS lesion [15] or recovery to be normal when translated into a diabetic nephropathy patient [16]. It is an ongoing debate whether MCD and FSGS represent different stages of one disease or are different disease entities [17].

The role of circulating factors has long been suspected in pathogenesis of FSGS due to several clinical observations, including the recurrence of FSGS in post-transplant patients (about 30% in adults), the induction of proteinuria in experimental animals by plasma fractions from FSGS patients, and the improvement of disease course after treatment with plasma exchange (PE), but with little success for searching the responsible factors [31]. In addition, the therapeutic benefits of immunosuppressive agents and RTX which inhibit cell-mediated immunity and the coincidence of INS in Hodgkin's disease indicate the role of immune disorder in MCD and FSGS [32]. Taken together, MCD and FSGS are likely to be systemic disorders, where circulating factors and/or immune dysfunction are the pathogenic culprit, subsequently causing podocyte injury (Figure 15.1).

Putative Circulating Permeability Factors

suPAR

Soluble urokinase-type plasminogen activator receptor (suPAR) has been suggested to be one of the pathogenic circulating factors [33–35]. The urokinase plasminogen activator surface receptor (uPAR) is a membrane-bound glycosyl-phosphatidylinisotol anchored protein present on multiple cells, including podocytes. In podocytes, uPAR could activate αvβ3 integrin signaling, inducing foot process effacement and proteinuria [33]. However, subsequent studies have suggested that suPAR may be a novel prognostic biomarker for chronic kidney disease, but does not appear to represent the permeability factor in FSGS [36].

CLCF1

Cardiotrophin-like cytokine factor 1 (CLCF1) is another candidate circulating factor which was detected in plasma from patients with recurrent FSGS. CLCF1 is a member of the IL6 family of cytokines. CLCF1 circulates as a heterodimeric cytokine, combining with cytokine receptor-like factor 1 (CRLF1) or soluble ciliary neurotrophic factor receptor alpha (sCNTFRa), which is an effector of the Janus kinase (JAK)/signal transducer and activator of transcription (STAT) signaling [37]. In podocytes, CLCF regulates the glomerular filtration barrier function through the JAK/STAT pathway [38]. In isolated rat glomeruli, CLCF1 increased albumin permeability (Palb) and an anti-CLCF1 monoclonal antibody was able to block the CLCF1-induced increase in Palb. Western blot analysis showed that CLCF1 upregulated phosphorylation of STAT3 in glomeruli. Inhibitors of JAK2 and STAT3 significantly blocked the effect of CLCF1 or FSGS serum on Palb. As such, albuminuria in FSGS might be related to qualitative or quantitative changes in the CLCF1-CRLF1 complex, and JAK2 or STAT3 inhibitors may be novel therapeutic agents to treat FSGS.

Anti-CD40 Antibody

The beneficial effects of RTX in MCD and FSGS suggest the role of autoantibodies in disease pathogenesis. By screening autoantibodies in pretransplant sera from 10 patients with recurrent FSGS and 10 without recurrent FSGS, auto-antibodies against 7 target proteins, including CD40 molecule, protein tyrosine phosphatase receptor O, tumor necrosis factor (TNF) receptor superfamily member 6, Chorionic gonadotropin β, Apoliprotein 2, P2Y purinoceptor 11 and Small nuclear retinoid × receptor α, were identified and validated. Among them, anti-CD40 antibody alone had the

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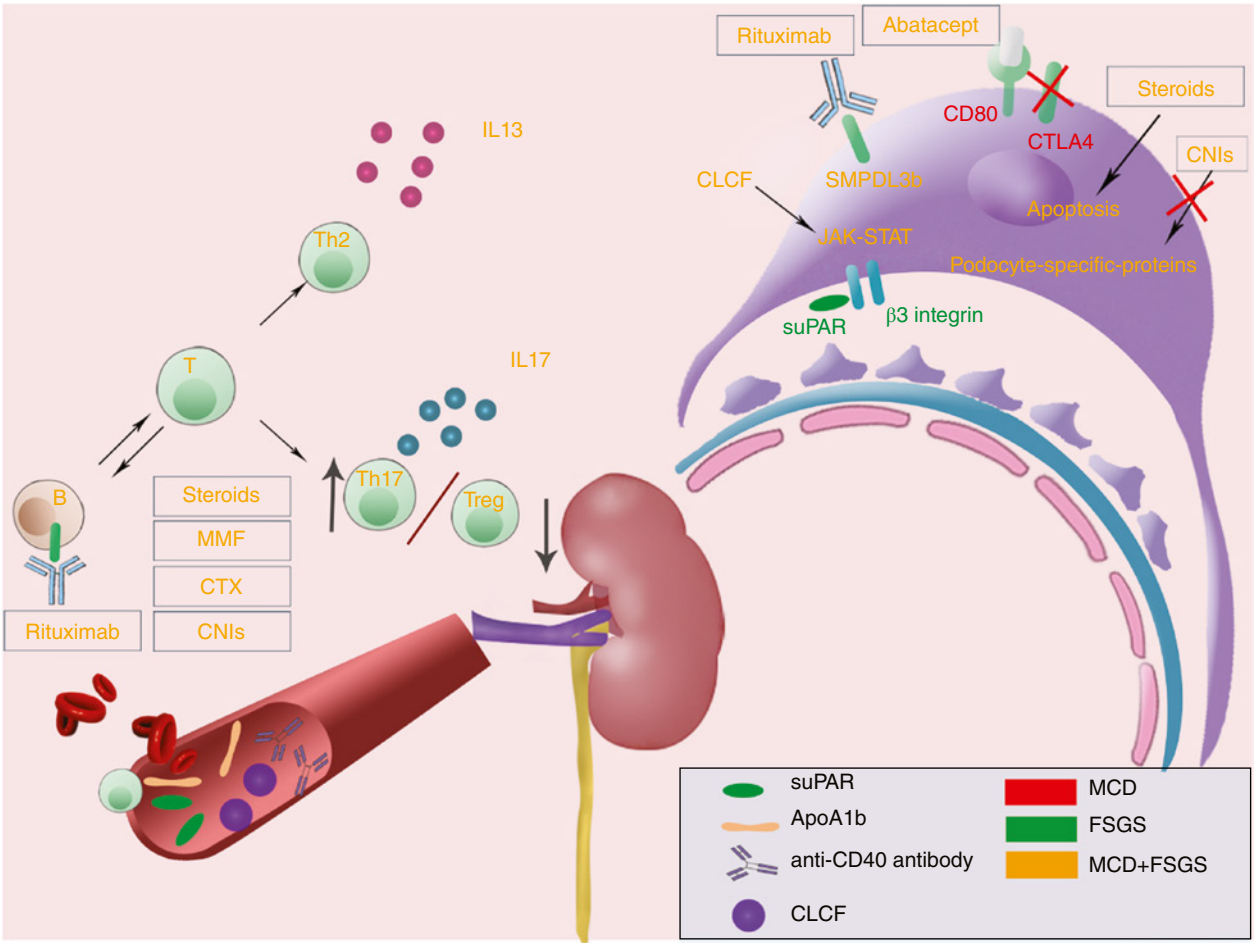

Figure 15.1 Pathogenesis of MCD and FSGS. The podocyte injury caused by circulating factors (suPAR, CLCF, ApoA1b, anti-CD40 antibody) and cytokines (IL13, IL17) secreted by abnormal interactions between T cells and B cells is crucial in disease pathogenesis. Except for their systemic effects, immunosuppressive agents (steroids, MMF, CTX, CNIs) and targeting treatment options (rituximab, abatacept) also show a direct effect on podocyte. Podocyte-related markers and products (CD80, suPAR) can be detected in the urine of patients with MCD and FSGS, providing a noninvasive technique for gathering information about the disease diagnosis and progression. Items mainly involved in MCD are shown in red, in FSGS are shown in green, and in both MCD and FSGS are shown in yellow.

best accuracy of 0.77 in predicting FSGS recurrence. During the phase of remission in recurrent FSGS patients after treatment of RTX plus cyclosporin (CsA), anti-CD40 antibody decreased accordingly. CD40 was stained on podocytes in patients with FSGS but not in normal human kidneys. Anti-CD40 antibody could cause podocyte injury directly by inducing cytoskeletal reorganization both in cultured human podocytes and in wild-type mice. The inhibition effects of monoclonal CD40-blocking antibodies, monoclonal suPAR clocking antibodies, or inhibitor of αvβ3 suggest an interaction between anti-CD40 antibodies and suPAR/β3 integrin pathway [39]. Independent validation in other recurrent FSGS cohorts is needed.

IL-13

The identity of the glomerular permeability factor in MCD has not been determined in humans. Data from animal models have implicated T helper type 2 (Th2)-derived cytokines, particularly interleukin (IL)-13. In rats, systemic overexpression of IL-13 results in albuminuria, hypoalbuminemia, and, on kidney biopsy, up to 80% podocyte foot process fusion by electron microscopy with similar pathologic findings as human MCD. In addition, T cells from patients with nephrotic syndrome spontaneously produce IL-13, while B cells express the IL-13 receptor. T cells from patients with relapsed MCD have increased expression of IL-13 compared with those from patients in remission.

microRNA

microRNAs (miRNAs) are important regulators of gene expression that suppress their target genes. miR-193a was significantly upregulated in isolated glomeruli from FSGS patients. Mechanistically it inhibits the expression of WT1,

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a transcription factor and master regulator of podocyte differentiation and homeostasis, which in turn leads to downregulation of genes crucial for the architecture of podocytes, such as podocalyxin (PODXL) and nephrin (NPHS1) [55]. The cause of the increased expression of miR-193a in podocytes of FSGS patients and the miRNA profiles in FSGS and MCD still needs to be addressed.

Immune Disorders

T Cells

Abnormal T cell dysfunction has long been implicated in the pathogenesis of MCD and FSGS. However, no consensus has yet been reached regarding a single cell subset. Some studies have shown elevated levels of IL2, some have suggested a relative predominance of a Th2 cytokine response (IL4), while others reported activation of Th1 cytokine response with increased interferon-γ. Urinary excretion of Th1 and Th2 cytokines cannot discriminate FSGS from MCD. However, urinary Th1 cytokines IL12 was associated with both global sclerosis and interstitial fibrosis, and IL2 and GM-CSF, Granulocyte-Macrophage Colony Stimulating Factor were significantly increased in FSGS patients resistant to treatment. Th2 cytokines, especially IL4, IL5, IL-8, IL10, and IL13, are implicated in frequent relapses of MCD [40, 41]. With the detection of new subsets of T cells, an increased Th17/Treg ratio was determined in adult patients with MCD and FSGS compared to normal subjects, which was associated with proteinuria [42]. Th17 cells are strong candidate drivers for steroid response in immune diseases [43], and the Th17/Treg imbalance returned to normal after effective corticosteroids therapy [42]. Dominance of infiltrating Th17 cells over Treg cells in the renal interstitial was also observed [44].

B Cells

The benefits of B cell-depleting therapy with RTX in MCD add a potential role of B cell in the pathogenesis of MCD. RTX performs its effects through suppressing the interactions between B cells and T cells, and restoring Treg cell populations to keep the Th17/Treg balance normal [45–49]. It also presents direct protective effects on podocyte cytoskeleton stabilization in a sphingomyelin phosphodiesterase acid-like 3b (SMPDL-3b)-dependent manner [50]. It partially prevented SMPDL-3b and ASMase downregulation that was observed in podocytes treated with the sera of patients with recurrent FSGS.

CD80

CD80/B7-1, a transmembrane protein usually expressed on B cells, nature killer cells, and antigen-presenting cells, also expressed on podocytes, which was proposed as a mechanism for proteinuria. It actives T cells by binding to receptor CD28, but inhibits T cell activation by binding to CTLA-4, cytotoxic T lymphocyte-associated antigen-4 expressed on regulatory T cells. CTLA-4 also downregulates CD80 and CD86 expression on APC, Antigen-presenting cells. In α3 integrin −/−, and nephrin −/− mice, CD80 is upregulated. In wild-type mouse models, injection of lipopolysaccharide (LPS) leads to CD80 upregulation in podocytes and proteinuria due to direct action of Toll-like receptor (TLR) ligands on podocytes. Adding tumor necrosis factor α (TNFα) to podocytes causes CD80 upregulation, which further interacts with Neph1 causing slit diaphragm disruption [51, 52]. CD80-deficient mice are protected from LPS-mediated podocyte injury. IL13 or microbial products via TLRs could be factors that induce CD80 expression on podocytes.

A two-hit podocyte immune disorder was postulated in MCD [53]. Initially, CD80 is induced by a microbial agent and/or T-cell cytokine. Impaired production of soluble CTLA4 by decreased circulating Tregs then induces persistent expression of CD80, which causes persistent proteinuria. Administration of abatacept, an inhibitor of CD80, appears to cure patients with severe nephrotic syndrome due to primary FSGS or recurrent FSGS after transplantation [54].

Others

Some other molecules participating in podocytopathy have also been suggested, such as nonmuscle myosin heavy chain-IIA (NMMHC-IIA) and RAP1GAP. NMMHC-IIA is located primarily at cell body and primary processes of podocytes. Expression levels of NMMHC-IIA were significantly decreased in puromycin aminonucleoside-treated rats and patients with idiopathic FSGS [56]. Increased podocyte expression of RAP1GAP, RAP1 GTPase Activating Protein was associated with loss of activated β1 integrin in vivo and in vitro by a mechanism that involves loss of RAP1-mediated activation of β1 integrin. Furthermore, preventing elevation of RAP1GAP levels in injured podocytes maintained β1 integrin–mediated adhesion and prevented cellular detachment [57].

Prognosis

Response to steroid therapy was the most important factor for preservation of renal function. In general, the majority of patients with MCD respond to steroids (80% sensitive rate with remission in 74%) and have preserved renal function for the long term, while FSGS is related to less steroid responsiveness (58% sensitive rate and 30% remission rate) [91]. However, more than two-thirds of adult patients

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with MCD experienced relapses, and up to a third of patients may become frequent relapsers or steroid-dependent. Younger onset age, steroid without cyclophosphamide treatment, and shorter treatment duration were independent risk factors for relapse [92]. Age is also a factor for steroid-related adverse events in MCD patients [93]. For MCD patients with FR or FSGS patients with less favorable outcome, there is increased early mortality owing to a higher risk of implications, including infections, thromboembolic events, and acute kidney injury (AKI).

Infection

Infectious complications are commonly seen in nephrotic patients due to mass proteinuria and/or use of immunosuppressive agents. Pneumonia is mostly common seen, and primary peritonitis, pneumonia, and cellulitis have also been reported [94, 95]. Accordingly, antibiotics should be applied as per regional practice. In addition, hepatitis B virus reactivation, tuberculosis, and parasite infection should be evaluated, if necessary, during immunosuppression.

Thromboembolic Events

Thromboembolic event is one of the most severe complications in NS. Hypercoagulable state in patients with NS could easily leads to venous thromboembolism (VTE) or arterial thromboembolism (ATE), the most common of which are deep vein thrombosis, renal vein thrombosis, and pulmonary embolism [96]. In a large retrospective cohort study, Mahmoodi et al. evaluated the VTE or ATE events in 298 consecutive patients with NS [97]. In the 10-year follow-up period, annual incidences of VTE and ATE were 1.02% (95% confidence interval [CI] 0.68–1.46) and 1.48% (95% CI 1.07–1.99), respectively. However, over the first 6 months of follow-up, these rates were as high as 9.85% and 5.52%, respectively. The ratio of proteinuria to serum albumin was associated with VTE, while eGFR and multiple classic risk factors for atherosclerosis, such as hypertension, diabetes, and smoking, were predictors of ATE.

AKI

AKI is a common complication of adult patients with MCD (up to 20–25%) [98] and patients with FSGS 39% [91]. It is an independent factor that delays the time to complete remission [99]. MCD-NS patients complicated with AKI had a more severe hypercoagulable state [100], which in turn increases the risk of thromboembolic events. For patients complicated with AKI, contemporary renal replacement therapy could be used, combining with corticosteroids.

Treatment

MCD

Corticosteroids

Corticosteroids remain the mainstay of first-line treatment of MCD in adults. There are still no large randomized controlled trials (RCTs) that provide evidence on the optimal agent, dose, and duration of corticosteroids that should be given. The evidence of using corticosteroids is based largely on extrapolation from RCTs in children [101, 102] and observational studies in adults [103–110]. The drug of choice is oral prednisone or prednisolone Box 15.1. As compared with MCD in children, adults tend to respond more slowly and the responsiveness is also less predictable. Prednisone was suggested to be used as a recommended dose of 1 mg/kg/day, not exceeding 80 mg, until CR (minimum 4 weeks to a maximum of 16 weeks). In the elderly some clinicians use a dose of 2 mg/kg given on an alternate-day basis, although no specific study has addressed the issue of similar efficacy and better tolerability. The issue of corticosteroid toxicity is well-recognized, but although weight gain, diabetes, and osteonecrosis are constantly cited regarding prolonged treatment with corticosteroids in adult MCD, very few published studies have provided specific long-term data on the rates of these complications.

Considering the adverse effects of long-term usage of high-dose corticosteroids, studies have examined enhanced corticosteroid therapy (short-term intravenous methylprednisolone with a low-dose of prednisone and/or another immunosuppressant) [109]. Two very early small RCTs compared intravenous methylprednisolone with or without subsequent oral prednisone to oral prednisone alone [111]. In one study, Yeung found no difference between intravenous methylprednisolone plus oral prednisone compared with oral prednisone alone for CR (relative risk [RR] 0.74, CI 0.50–1.08) in 18 adult patients with MCD. In the other study, Imbasciati observed that oral prednisone, compared with short-course intravenous

Box 15.1 Corticosteroid Agents (Potency Relative to Prednisone)

Oral agents
- Prednisone [1]
- Prednisolone [1]

Intravenous agents
- Methylprednisolone [1.25]

Subcutaneous agents
- ACTH (Adrenocorticotropic hormone)

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methylprednisolone, increased the number of subjects who achieved CR (RR 4.95, CI 1.15–21.26) in 22 patients with MCD. Given the limited number of patients, these two studies might be underpowered and inferiority of intravenous methylprednisolone could not be excluded. Subsequent observational studies suggested that intravenous methylprednisolone and prednisolone use was significantly associated with early remission and lower incidence of relapse compared with prednisolone use alone [108, 109], which was suggested in an Italian RCT in pediatric patients with MCD [112].

In a recent multicenter RCT, tacrolimus (TAC) monotherapy or oral prednisone (1 mg/kg/day, maximum 80 mg/day) after short-term intravenous methylprednisolone (0.8 mg/kg/day) for 10 days showed remission rates of 98.3% (55/56) and 96.2% (51/53), respectively. Although there was no statistically significant difference in remission rates, mean time to remission, and relapse rates between the two groups, adverse events occurred more frequently in the prednisone group than in the TAC group (128 vs. 81) [113]. In a retrospective study, treatment with intravenous methylprednisolone (0.5 or 1.0 g/day for 3 days) followed by oral cyclosporine (2–3 mg/kg/day) and low dose of prednisolone (30 mg/day) showed 100% complete remission rate compared to 85.7% in patients treated with intravenous methylprednisolone followed by oral prednisolone (0.4–0.8 mg/kg/day) and 69.2% in patients treated with oral prednisolone (0.6–1.0 mg/kg/day) alone during the 9-month follow-up. The adverse effects caused by prednisolone were fewer [114].

Although more than 90% of adult patients with MCD achieve CR, about 50% of them experience relapses during the disease course [94, 103, 104, 107, 110]. For patients with infrequent relapse, optimal corticosteroid dose for relapse is still unclear. The KDIGO guidelines recommend the same initial dose and duration. One observational study in children and one in adults suggested lower dose corticosteroid therapy might be helpful to improve the quality of life of patients [110, 115]. For patients with FR or SD, corticosteroid-sparing agents such as cyclosporin (CsA), cyclophosphamide, and mycophenolate mofetil (MMF) are usually needed (discussed in the following sections). A small observational study tested the effects of adrenocorticotropic hormone (ACTH) gel (80 units subcutaneously twice weekly) in 15 subjects with resistant glomerular diseases (MCD = 2, FSGS = 3) for 6 months. One subject with resistant FSGS achieved CR and one subject with resistant MCD achieved PR but relapsed within 4 weeks of stopping ACTH [116]. The evidence should be studied further in controlled trials against currently available therapies for resistant disease.

Alkylating Agents

Only a few patients have been treated with alkylating agents (cyclophosphamide or chlorambucil) in the initial treatment of MCD [106, 117, 118] Box 15.2. Alkylating agents are indicated in multirelapsing cases more than for SR forms (opinion) [103], although true SR is rare in true MCD, that is, cases in which a repeat renal biopsy carried out after 4 months of unsuccessful corticosteroid therapy still shows MCD. In most cases the second histopathologic examination discloses lesions of FSGS that had been overlooked or not sampled on the first biopsy, or had not yet appeared at the onset of NS, which explains the initial failure of corticosteroids [103, 105, 106, 119, 120].

Despite the lack of studies specifically related to adult multirelapsers, it is likely that cytotoxic agents result in prolonged remissions, as shown in RCTs in children. Cyclophosphamide, at 2–3 mg/kg/day, is more commonly used than chlorambucil, without clear evidence of the superiority of one over the other. It should be administered orally and not in the form of intravenous pulses, and presumably, considering the experience acquired with childhood onset cases, for 8 weeks. Alkylating agents entail known hazards of hematologic, infectious, and oncologic side effects, but quantifying these risks is not possible given the available data. In men and women the risk of sterility is significant if the course is prolonged, and the risk increases with increasing age at the time of onset of the therapy.

CNIs

CsA

CsA has been used in adults with MCD since 1986 [1] Box 15.3. Its side effects include hypertension, tremor, gingival hyperplasia, and hypertrichosis. Conversely, CsA has the advantage of not being cytotoxic, does not induce sterility, and entails fewer metabolic disturbances. These reasons may justify its use as first-line treatment in patients at risk of diabetes, osteonecrosis, or infertility. Aside from clinical scenarios in which corticosteroids are contraindicated

Box 15.2 Alkylating Agents

Cyclophosphamide
Chlorambucil

Box 15.3 Calcineurin Inhibitors

Cyclosporine (CsA)
Tacrolimus (TAC)

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[121], CsA first-line monotherapy has been used in many case series (level IV studies) with very low dose [122]. One such study [121] included 86 adult patients with MCD and NS that were resistant to conventional therapy or were SD or multirelapsers. They were treated with the Sandimmune formulation at a dose of 5.18 ± 0.94 mg/kg/day. Superior efficacy was reported in SD patients (CR in 73% of cases and PR in 14%) compared to those who were SR (30% and 26%, respectively). Serum creatinine levels remained stable during CsA treatment. These patients were not all CsA dependent, as ~20–25% were progressively tapered off after 2 years without relapsing [123]. Combination therapy with CsA and corticosteroid agents might further enhance the efficacy and with less corticosteroid toxicity as mentioned above [114], suggesting an additional benefit of lower exposure to corticosteroids. A RCT performed in 52 adult patients with the first relapse of MCD noted that remission was achieved sooner in patients treated with CsA plus 0.8 mg/kg/day prednisone compared to patients receiving only 1 mg/kg/day prednisone [124].

One of the main safety concerns of CsA therapy in INS is the potential for nephrotoxicity. This is a class effect common to all CNIs, including TAC [125, 126] Box 15.3. Previous studies indicated that the dose and type of primary renal disease are two elements to keep in mind when interpreting a decline in renal function [123].

A problem that has appeared since 1999 is that of formulation. Most publications mention "cyclosporine" and do not specify whether they are discussing Sandimmune or Neoral or a generic form of the drug, which may be important because it is known that the better pharmacokinetic profile of Neoral may lead to better efficacy and hence a distinct reduction of dose [125] below the maximum of 5 mg/kg/day recommended for Sandimmune [123].

TAC

Given the FR after withdrawal and the risk of renal toxicity after long-term therapy with CsA, there are several studies focus on detecting the efficacy of TAC to induce CR in adults with MCD. TAC, like CsA, is a CNI that inhibits T-cell-driven elaboration of cytokines. It shows more potent cytokine suppression and seems to cause less toxicity than CsA. In a recent multicenter RCT, TAC monotherapy following short-term intravenous methylprednisolone (0.8 mg/kg/day) for 10 days showed comparable remission rates, remission rates, mean time to remission, and relapse rates with the conventional oral prednisone regimen, but fewer adverse events [113]. In one pilot study, the cumulative CR rates of patients treated with oral TAC (0.05 mg/kg twice daily) and low-dose prednisolone (0.5 mg/kg/day) were 7.7% (1/14), 64.2% (9/14), 71.3% (10/14), 92.9% (13/14), and 100% (14/14) at 1, 2, 4, 8, and 20 weeks respectively [127]. In one small observational study, TAC (0.05–0.1 mg/kg/day) combined with prednisone (0.5 mg/kg/day) showed a remission rate of 90.9% (10/11) with a CR rate of 72.7% (8/11) in CsA-resistant and -dependent adult MCD patients within 2 months [128].

MMF

Studies of MMF in the treatment of MCD in adults are few and are limited to case series and reports [129–131]. Considering the encouraging results obtained in childhood nephrosis, MMF may have a place in the treatment of adult MCD, but so far evidence either supporting or refuting its use is absent.

RTX

RTX, a chimeric monoclonal antibody directed against CD20, is a potential effective and safe treatment in adults with MCD Box 15.4. The use of RTX in adults with FR and immunosuppression-dependent MCD has been reported in case reports [132–134] and small observational studies [135–138] in reducing relapses and sparing immunosuppression. A prospective, multicenter, off–on trial evaluated the efficacy of RTX and rate of recurrences in a cohort of 10 children and 20 adults with FR MCD and FSGS after administration of RTX and discontinuation of immunosuppressants. One year after, all 30 patients were in remission and half of them never presented any recurrence during the follow-up. The total number of relapses, the per-patient annualized relapse rate, the per-patient corticosteroid maintenance median dose, and the median cumulative dose to achieve relapse remission were reduced significantly after treatment with RTX. Renal function improved in all subjects, especially in children and in FSGS subgroups [139]. Similar results were reported extending the observation period to more than 2 years, demonstrating a long-lasting effect of RTX [136, 140–142]. One very small observational study has reported the efficacy of RTX as a first-line therapy in six adult-onset MCD cases [143]. In future RCTs, detecting the efficacy of RTX as both first-line and second-line treatment with extended follow-up will add important information regarding its optimal treatment, relapse, and safety.

Box 15.4 Monoclonal Antibodies

Rituximab
Fresolimumab
Adalimumab
Abatacept

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Summary

MCD is not uncommon in adults and may assume a multirelapsing course. The majority of patients respond to corticosteroids with CR, but this may require 4 months of treatment, compared with 6–8 weeks in children, with the attendant hazards of corticosteroid toxicity. Enhanced corticosteroid therapy (short-term of intravenous methylprednisolone with a low dose of prednisone and/or with another immunosuppressant) might be alternative option to reduce corticosteroid toxicity. In selected cases, low-dose CNIs can be considered an alternative to corticosteroids, with very little nephrotoxicity. SR may be due to an initially missed diagnosis of FSGS, and resistance should be considered an indication to verify the diagnosis by a repeat kidney biopsy. The place of MMF in the treatment of adult MCD remains to be determined. For patients with FR or conventional treatment-resistant, RTX is a promising option, although the current evidence is limited to observational studies. The strength of evidence supporting these statements is low or very low, being largely based on case series and observational studies (RCTs tending to revise treatment recommendations are summarized in Table 15.4).

FSGS

All forms of FSGS require treatment, irrespective of the histopathologic variant [4, 5, 8, 144]. The goal of therapy is to reduce, if not eliminate, proteinuria. Inducing even a PR reduces the rate of deterioration in renal function [6]. Corticosteroids remain the first-line treatment. Response to corticosteroids is also the best indicator of a better long-term prognosis. In case of failure, a panoply of immunosuppressive drugs have been tried, including new immunosuppressive agents used in solid organ transplantation. A few recent publications on RTX [145] indicate that the anti-CD20 monoclonal antibody may inconsistently obtain remission in cases of FSGS, especially when the NS relapses after renal transplantation.

Corticosteroids

Current consensus remains that corticosteroids with full dose and extended period of time are the first-line of therapy in nephrotic FSGS. In the absence of any RCT data, the evidence mainly based on several observational studies with remission rates ranging from 30% to 60% [20, 146, 147]. The initial

Table 15.4 Summary of findings: treatment of adult minimal change disease (MCD).

Outcomes	No. of participants (no. of studies)	Absolute effect per 1000 patients treated for 1 year (95% CI)	Relative risk (95% confidence interval)	Certainty of the evidence (GRADE)	Conclusion
Intravenous methylprednisolone/TAC vs. intravenous methylprednisolone/prednisone [113]					
Remission rate (CR or PR)	109 (1)	Not estimable	1.02 (0.96–1.09)	Low ●○○○	TAC is noninferior to prednisone after short-term intravenous methylprednisolone
Relapse rate	106 (1)	Not estimable	0.93 (0.62–1.39)	Low ●○○○	TAC and prednisone show similar relapse rates
Adverse event rate	109 (1)	Not estimable	0.83 (0.71–0.98)	Low ●○○○	Adverse events occur more frequently in the prednisone group
CsA/prednisolone (0.8 mg/kg/day) vs. prednisolone (1 mg/kg/day) [124]					
Remission rate (CR or PR)	52 (1)	Not estimable	1.25 (1.01–1.55)	Low ●○○○	Low-dose CsA allows the prednisolone dose to be reduced as compared to therapy with prednisolone alone
Relapse rate	52 (1)	Not estimable	1.20 (0.41–3.47)	Low ●○○○	Combining with or without CsA show similar relapse rates
Adverse event rate	—	—	—	—	Adverse event was not analyzed

CI, confidence interval; CR, complete remission; CsA, cyclosporin; PR, partial remission; TAC, tacrolimus. GRADE assessment of the certainty of the evidence: High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different* is low. Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different* is moderate. Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different* is high. Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different* is very high. **Substantially different = a large enough difference that it might affect decision-making*. Pooled analyses were not performed due to the heterogeneity of the data.

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response to treatment in adults with FSGS was analyzed by Korbet et al. [144, 148, 149]. The trend before 1980 was to treat for a short time and with low doses of corticosteroids. The highest CR rates, >30%, were observed in cases treated for >5 months, and the lowest, ≤20%, were seen in patients treated for≤2 months. Thus, corticosteroid treatment must be sufficiently long. Full-dose (1 mg/kg/day) prednisone is given for 8–12 weeks, followed in case of remission, even partial, by slow tapering over months to avoid a "rebound" relapse [150]. CR portends a favorable outcome, comparable to that of corticosteroid-responsive MCD [18]. However, a minority of patients with nephrotic FSGS achieve stable remission after tapering corticosteroids to complete withdrawal. Most cases are SD, usually to a high threshold dose. This poses a serious problem, as pursuing indefinite treatment with a high-maintenance dose leads to corticosteroid side effects. Corticosteroid dependency or resistance leads to the need to consider other treatment options aimed at reducing proteinuria, but which trade corticosteroid toxicity for other complications.

In a pilot study, 24 nephrotic patients with idiopathic FSGS, including six SD and 15 SR, were treated with ACTH gel (median dose was 80 units injected subcutaneously twice weekly). After treatment, 29% (7/24) patients showed remission. All remitters had SR ($n = 5$) or SD ($n = 2$) FSGS. ACTH treatment might be an alternative option for SR or SD patients with FSGS, although the response rate is low [151]. In a observational study, 20 patients of post-transplant recurrent and de novo FSGS resistant to conventional therapy with therapeutic PE and RTX received ACTH, and 50% (10/20) of patients achieved CR or PR [152].

Alkylating Agents

The best indication for use of an alkylating agent is the case of a SD or multirelapsing patient, which is rare in nephrotic FSGS. Some studies included patients treated with a combination of cyclophosphamide or chlorambucil and corticosteroids. A RCT in 57 patients by Heering et al. [153] included 23 patients treated for 6 months with corticosteroids and chlorambucil. They achieved 17% CR and 48% PR. Five of the 23 progressed to end-stage renal disease (ESRD). The contributions of other studies to treatment recommendations about alkylating agents are uncertain, such as Martinelli et al.'s case series [154]. In short, there is no strong evidence to recommend alkylating agents in the treatment of FSGS.

CNIs

CsA

CsA has been used for three decades in the treatment of FSGS. It has been shown that its efficacy is greatly increased by a combination with low-dose corticosteroids [121]. Combination of CsA and corticosteroids remains the mainstay of treatment, with good tolerability when CsA dose is low. A retrospective observational study compared high-dose oral prednisone (1 mg/kg/day) with low-dose prednisone (0.5 mg/kg/day) in combination with CsA (3 mg/kg/day) or azathioprine (2 mg/kg/day) as initial treatments. Low-dose prednisone was given to 16 patients with obesity, bone disease, or mild diabetes. Remission rates were comparable; 63% for prednisone ($n = 9$), 80% for prednisone plus azathioprine ($n = 6$), and 86% for prednisone plus CsA ($n = 10$) [155]. Using the Glomerular Disease Collaborative Network (GDCN) Registry, Laurin et al. [156] showed that early use of immunosuppressive therapy with CNIs and/or corticosteroids was associated with improved renal outcome compared with no immunosuppression in 458 adults and children with primary FSGS (HR 0.49, 0.28–0.86). Although there was a trend toward greater survival among patients treated with CNIs, the superiority of CNIs over corticosteroids alone remained unproven.

For SD or SR patients, two RCTs noted the efficacy of CsA [157, 158]. Remission rates are 69% and 60%, but relapse after CsA withdrawal occurred in 61% and 69%, respectively. In the former study [157], CsA (3.5 mg/kg/day) was combined with low-dose prednisone (0.15 mg/kg/day). Long-term renal function was significantly better preserved in the CsA group, suggesting that low-dose CsA-induced PR reduces the rate of progression of nephrotic FSGS patients to renal insufficiency. A comparison was made in 226 patients treated for SR-NS (the majority were FSGS with some cases of MCD), with 127 receiving CsA alone and 103 receiving CsA plus corticosteroids. The proportions of patients with CR, PR, and failure were, respectively, 14% versus 24%, 12% versus 24%, and 74% versus 52%. Thus, CsA combined with low-dose corticosteroids can be considered both an immunosuppressive drug and a steroid-sparing agent to treat resistant forms of FSGS.

Another case series [121] was based on 68 patients treated with 5.18 ± 0.94 mg/kg/day of CsA (Sandimmune formulation). The results on NS were 14 CR (21%), 19 PR (28%), and 35 failures (51%). Other case series have comprised patients treated with CsA (among other immunosuppressants) and support the beneficial effect of CsA for inducing at least PR in nephrotic FSGS.

TAC

There are no RCTs for this medication in FSGS. So far, the experience acquired is mainly in CsA-resistant or -dependent patients. Another small observational study used TAC monotherapy as initial treatment in six patients, and all six patients achieved remission after 6.5 ± 5.9 months [159].

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Sirolimus

Autophagy was suggested to be involved in maintaining cellular health in podocyte and autophagic exhaustion was suggested to be central deriver of podocyte injury in FSGS [160]. However, translating this finding into clinical practice dampened the enthusiasm, since treatment with mammalian target of rapamycin (mTOR) inhibition, sirolimus, appears to be ineffective and potentially harmful. The current experience with this drug is controversial and inadequate to allow recommendations on its use in FSGS [161].

MMF

The current experience regarding MMF in the treatment of FSGS seems more or less encouraging [162–164]. A recent RCT compared CsA to the combination of MMF and high-dose dexamethasone in children and young adults with SD-FSGS [165]. No difference in treatment effectiveness was shown between the two groups, and adverse effects were comparable. However, the limitations of this study, regarding the limited number of patients (2.5 patients per center) and the heterogeneous population (children and adults, different ethnity origin), make it difficult to indicate that CsA treatment might be superior.

Monoclonal Antibodies

RTX

The efficacy of RTX in adult-onset FSGS remains conflict [166]. Case series suggest RTX therapy could increase the CR or PR rates, decrease the relapse rate, and stop the concomitant therapy to include corticosteroids and immunosuppressive agents in patients with a severe disease course, a failure of previously used immunosuppressive regimens, and kidney transplantation recipients with recurrent FSGS [134, 167–171]. In a 2-year observational study, a high dose of RTX (eight weekly doses of 375 mg/m^2) failed to improve proteinuria in seven out of eight patients [172]. A multicenter off–on trial primarily evaluated the effects of RTX followed by immunosuppressive agent withdrawal on disease recurrence in 10 children and 20 adults MCD/MesGN ($n = 22$) or FSGS. Overall, the evidence of RTX in FSGS is mainly drawn from case reports or in a retrospective manner with various treatment modes, and several questions remain to be answered, such as dose, duration, and long-term follow-up outcomes.

Fresolimumab

In a phase 2 double-blind, placebo-controlled, randomized study of Fresolimumab in patients with SD primary FSGS, patients received placebo ($n = 10$), fresolimumab 1 mg/kg ($n = 14$), and fresolimumab 4 mg/kg ($n = 12$), respectively. However, none of the patients achieved partial (50% reduction) or complete (<0.3 g/24 h) remission of proteinuria. This small underpowered study has not provided any conclusions yet [173].

Adalimumab

In the Novel Therapies for Resistant FSGS (FONT) phase II study, 21 patients with resistant FSGS were assigned to adalimumab (an anti-TNFα monoclonal antibody), glactose or standard medical therapy. While none of the adalimumab-treated subjects achieved the primary outcome, two subjects in the galactose and two in the standard medical therapy arm had a 50% reduction in proteinuria without a decline in eGFR [174].

Abatacept

Considering the role of CD80 in pathogenesis of MCD, an inhibitor of CD80, abatacept, was suggested to be used in disease treatment. Abatacept (CTLA-4 immunoglobin) is a soluble fusion protein that consists of the extracellular domain of human CTLA-4 linked to the modified Fc portion of human IgG1. It significantly reduced the proteinuria in RTX-resistant recurrent FSGS after transplantation and in one patient with SR primary FSGS with CD80 staining of podocytes in kidney-biopsy specimens [175]. However, the effectiveness of abatacept was not replicated in subsequent studies [176, 177]. Larger RCTs are required to determine its efficacy and safety in the future.

Summary

Nephrotic FSGS, irrespective of its histopathologic variant, is always an indication for a course of full-dose corticosteroids, preferably prednisone (opinion), for a minimum of 4 months prior to labeling the SD patient (opinion). CR portends an excellent prognosis. PR is beneficial, both clinically and in terms of preservation of renal function. In the case of SD, the use of a combination of CsA and low-dose corticosteroids obtains partial or, more rarely, CR in about 50–70% of patients, with a definite advantage regarding long-term preservation of renal function. Among the various other immunosuppressants tried in the treatment of FSGS, MMF has the advantage of no nephrotoxicity, but the studies to date, although positive, have been small and pilot in nature. With our understanding of disease pathogenesis, clinical trials of targeting therapy options with more efficacy and fewer adverse effects are ongoing (RCTs tending to revise treatment recommendations are summarized in Table 15.5).

Plasmapheresis

The rationale for treating nephrotic FSGS with PE is based on the concept of a glomerular permeability factor, postulated by Shalhoub in 1974 [178], and despite this

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Table 15.5 Summary of findings: adult focal segmental glomerulosclerosis (FSGS).

Outcomes	No. of participants (no. of studies)	Absolute effect per 1000 patients treated for 1 year (95% CI)	Relative risk (95% CI)	Certainty of the evidence (GRADE)	Conclusion
CsA vs. MMF/dexamethasone [165]					
Remission rate (CR or PR)	138 (1)	Not estimable	1.38 (0.91–2.09)	Low ●○○○	CsA and MMF/dexamethasone show similar remission rate in patients with steroid-resistant FSGS
Relapse rate	48 (1)	Not estimable	2.14 (0.84–5.45)	Low ●○○○	CsA and MMF/dexamethasone show similar relapse rate in patients with steroid-resistant FSGS
Adverse event rate	138 (1)	Not estimable	Not estimable	Low ●○○○	CsA and MMF/dexamethasone show similar adverse event rate in patients with steroid-resistant FSGS
CsA/prednisolone vs. intravenous methylprednisolone [158]					
Remission rate (CR or PR)	25 (1)	Not estimable	1.69 (0.92–3.12)	Low ●○○○	There was no significant difference in remission rate between the two groups
Relapse rate	15 (1)	Not estimable	Not estimable	Absent	A high relapse rate (69%) occurs after CsA withdrawal
Adverse event rate	25 (1)	Not estimable	Not estimable	Absent	A high adverse event rate (25%) receiving occurs in the intravenous methylprednisolone group
CsA/low-dose prednisone vs. prednisone [157]					
Remission rate (CR or PR)	49 (1)	Not estimable	8.85 (1.22–63.92)	Moderate ●●○○	There was a significant increase in the number of patients with remission in the CsA/low-dose prednisone group
Relapse rate	35 (1)	Not estimable	Not estimable	Absent	A high relapse rate (60%) occurs in CsA/low-dose prednisone group by week 78
Adverse event rate	49 (1)	Not estimable	Not estimable	Absent	Nausea and vomiting were reported in one patient after in the CsA/low-dose prednisone group

CI, confidence interval; CR, complete remission; CsA, cyclosporin; MMF, mycophenolate mofetil; PR, partial remission; TAC, tacrolimus. GRADE assessment of the certainty of the evidence: High; This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different* is low. Moderate; This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different* is moderate. Low; This research provides some indication of the likely effect. However, the likelihood that it will be substantially different* is high. Very low; This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different* is very high. **Substantially different = a large enough difference that it might affect decision-making*. Pooled analyses were not performed due to the heterogeneity of the data.

factor being the subject of numerous publications, much remains uncertain about it [179]. There is no evidence that PE modifies the course of FSGS, outside of the particular case of relapse of NS in a kidney transplant recipient [144]. Based on the concept of a "circulating factor," PE has been advocated to remove it, reduce proteinuria, and avoid the progression to renal insufficiency, but there is little evidence for or against its use. In 2001 Bosch and Wendler [180] concluded, in a review of extracorporeal plasma treatment in primary and recurrent FSGS, that there was only poor evidence to support its use, and no significant additional data have been added since that time. A systematic review and meta-analysis of 77 case reports and case series noted that 71% of patients achieved CR or PR after treatment with PE [181].

Similarly, plasma protein adsorption on columns coated with staphylococcal protein A [182] does not seem to remove specifically the elusive circulating factor responsible for the proteinuria, as this experimental protocol also reduces proteinuria in other glomerulopathies [183].

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Pregnancy

INS occurring during pregnancy poses a unique situation. The majority of the data relative to the effects of immunosuppressive treatment in pregnancy are based on post-kidney transplantation reports. High-dose corticosteroids entail a risk to the fetus [184]. Alkylating agents are contraindicated. In the CsA era, case reports, center reports, and registry data have supported the concept that successful pregnancy outcomes are possible for mother and newborn in the presence of stable graft function and well-controlled maternal comorbidities, such as hypertension. While the risks of prematurity and low birth weight are greater than those seen in the general population, there has been no increase in the malformation rate of newborns. Successful pregnancy outcomes have been reported in nonrenal CsA recipients as well [185–187]. The available experience with MMF has been limited to organ transplantation [185–187]. Two newborns with malformations were noted in a limited case series with MMF exposure, but other factors may have also been at play. The use of MMF during pregnancy continues to be an unresolved issue. In summary, CsA seems to be the less toxic agent to treat a case of INS during pregnancy, but the data are weak.

Conclusion

Both similarities and differences regarding the clinical characteristics, pathogenesis, treatment responses, and outcomes were shown between MCD and idiopathic FSGS. There is still a debate on whether they are different phenotypes of the same disease or two entities. Corticosteroids and CNIs remain the mainstay treatment in MCD and idiopathic FSGS, while RTX seems to be a promising alternative. Clinicopathological studies and experimental models support the pathogenesis that MCD and FSGS are podocyte disorders caused by circulating factors and/or immune dysfunction. Lifting the veil of these factors and the underlying mechanisms provides diagnostic, therapeutic, and prognostic insights.

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16

Membranous Nephropathy

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Introduction

Idiopathic membranous nephropathy is a common immune-mediated glomerular disease and remains the leading cause of nephrotic syndrome (NS) in Caucasian adults. Secondary forms may account for up to one-third of cases and are associated with autoimmune diseases (e.g. systemic lupus erythematosus), infections (e.g. hepatitis B and C), medications (e.g. nonsteroidal anti-inflammatory drugs [NSAIDs], D-penicillamine, gold), and neoplasias (e.g. carcinomas) [1]. The association with malignancy increases with age, reaching up to 20% in patients over the age of 60. Because idiopathic and secondary forms have similar clinical presentations, the designation of idiopathic is made only after ruling out secondary causes by a careful history, physical examination, and laboratory evaluation. It is crucial to rule out secondary causes of membranous nephropathy because the management is directed toward removing or correcting the underlying cause.

Natural History

Membranous nephropathy is a chronic disease, with spontaneous remission and relapses. There is great variability in the rate of disease progression, and the natural course is difficult to assess in part due to heterogeneous criteria for indication of biopsy and genetic and geographic disease biology [2–4]. Spontaneous remissions occur in up to 30% of cases, usually in the first 2 years after presentation, but may occur any time. The proportion of patients going into spontaneous remission is much lower when patients are selected who have higher grades of proteinuria at presentation, for example proteinuria of >8 g/24 h. The remaining two-thirds of patients who do not undergo spontaneous remission generally divide equally into either those with persistent proteinuria who will maintain renal function long term or those patients who will progress to kidney failure. In Caucasian patients with nephrotic syndrome, 10-year kidney survival of <70% has been reported [2, 5–8].

Because of its high incidence rate, membranous nephropathy remains the second or third leading cause of end-stage kidney disease (ESKD) among the primary glomerulonephritis types [9]. Even patients who do not progress but remain nephrotic are at an increased risk for life-threatening thromboembolic and cardiovascular events. A rapid change in either the degree of proteinuria or the rate of loss of renal function, especially in a previously stable patient, should raise the possibility of a superimposed condition, for example interstitial nephritis, crescentric glomerulonephritis, sepsis, or renal vein thrombosis.

Clinical Manifestations

Membranous nephropathy affects patients of all ages and races, but it is more common in men than women by a 2 : 1 (male:female) to 3 : 1 ratio. Idiopathic membranous nephropathy has a peak incidence during the fourth and fifth decades of life, and is relatively uncommon in patients under 20 years. At presentation, 60–70% of patients will have nephrotic syndrome. The presence of microscopic hematuria is common (30–40%), but macroscopic hematuria and red cell casts are rare and suggest a different histopathology. At presentation, the great majority of patients

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are normotensive, with only 10–20% having hypertension and only a small fraction of patients (<10%) having significant renal insufficiency. Risk of thromboembolism is very high in the first 6 months [10]. The incidence of venous thromboembolism is 9.85% and arterial thrombembolism is 5.52%. The risk is higher if serum albumin <2.8 g/dl [11].

Pathogenesis

Phospholipase A_2 receptor

In the past decade, the understanding of the pathogenesis of idiopathic membranous nephropathy has substantially improved. In 2009, phospholipase A_2 receptor (PLA2R) was identified as the major antigen responsible for autoantibody binding in idiopathic membranous nephropathy [12]. PLA_2R is a transmembrane receptor that is highly expressed in glomerular podocytes and was initially identified in 70% patients with idiopathic membranous nephropathy [12]. Subsequent studies from various cohorts have shown that PLA_2R antibodies are positive in 50–80% of patients with idiopathic membranous nephropathy [13–18]. PLA_2R antibodies are uncommon in patients with membranous nephropathy associated with malignancies. There is genetic polymorphism in PLA_2R-associated membranous nephropathy, which is linked with HLA-DQA1 risk alleles [19, 20]. Furthermore, the presence of HLA DQA1*05 : 01 and DQB1*02 : 01 alleles is associated with higher PLA_2R antibody levels [21].

Thrombospondin Type-1 Domain-Containing 7A

Thrombospondin type-1 domain-containing 7A (THSD7A), like PLA_2R, is a protein highly expressed in podocytes and was identified in European and North American patients with anti-PLA_2R-negative idiopathic membranous nephropathy but not in healthy controls or patients with other glomerular diseases [22]. It occurs in 2.5–5% of all patients with idiopathic nephropathy, which corresponds to 8–14% of patients who are seronegative for anti-PLA_2R antibodies. A recent meta-analysis of 10 studies involving 4121 patients showed prevalence of THSD7A was low at 3% (95% CI 2–4%) of all patients with idiopathic membranous nephropathy, which corresponded with 10% (95% CI 6–15%) of anti-PLA_2R antibody negative patients [23]. However, this meta-analysis was limited by a small number of studies and sample size. Cancer may be more common in patients with THSD7A antibodies [24]. Further studies to elucidate the role of THSD7A as a marker of prognosis and response to therapy are required. Antibodies against PLA_2R and THSD7A coexist but only occasionally [25].

Predicting Factors

Evaluating the prognosis is critical in making decisions regarding treatment [26–28]. Individual factors, such as advanced age, male gender, and selected biopsy findings (e.g. degree of interstitial fibrosis, glomerulosclerosis, vascular damage, or glomeruli with focal segmental glomerulosclerosis), are predictors of prognosis and/or response to immunosuppressive therapy [29]. In addition, the degree of proteinuria may also predict those who are most likely to progress. Pei et al. observed a 47% risk for progression in patients with proteinuria of >4 g/24 h for longer than 18 months and a 66% risk in patients with proteinuria of >8 g/24 h for more than 6 months [30]. The degree of renal impairment at presentation has also been found to correlate with long-term renal survival.

PLA_2R antibodies appear to correlate with disease activity, response to therapy, and prognosis, which may allow them to be used as biomarkers for assessing treatment efficacy [21, 31–33]. Additionally, higher antibody levels are linked to a higher risk of declining renal function, suggesting that these affected individuals may benefit from earlier initiation of immunosuppression [21]. Conversely, favorable outcomes have been shown in patients who do not have PLA_2R antibodies. Spontaneous remission rates are higher in patients with low (negative or lowest tertile) antibody levels (79%, HR 2.72, 95% CI 1.22–6.09, $P = 0.02$) compared to patients with higher antibody levels [33]. In another study of 28 seronegative patients, 91% had spontaneous remission (7 out of 10 had complete remission [CR]) [34].

Response Measurements

The goal of treatment is to achieve either CR or partial remission (PR). Definition of CR or PR is reported differently by different studies. However, the definition reported by Kidney Disease Improving Global Outcome (KDIGO) seems to be more widely agreed upon [35]. KDIGO defines CR as urinary protein excretion <0.3 g/day (urinary protein to creatinine ratio < 300 mg/g or < 30 mg/mmol) accompanied by a normal serum albumin concentration and a normal serum creatinine. PR is defined as urinary protein excretion <3.5 g/day (urinary protein to creatinine ratio < 3500 mg/g or < 350 mg/mmol) and a 50% or greater reduction from peak values accompanied by an improvement or normalization of the serum albumin concentration and stable serum creatinine.

About 30% of membranous nephropathy cases will relapse subsequent to CR [36]. The great majority who do, however, will relapse to subnephrotic-range proteinuria and will have stable long-term function. PR has been also recognized as a

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specific outcome. A review of 350 nephrotic patients with membranous nephropathy found that the 10-year renal survival was 100% in the CR group, 90% in the PR group, and 45% in the no-remission group [37]. Patients with CR or PR have a similar rate of decline: −1.5 ml/min/year in the CR group and −2 ml/min/year in the PR group. In contrast, the no-remission group lost glomerular filtration rate (GFR) at a rate of −10 ml/min/year. Thus, both CR and PR appear to be excellent predictors of long-term renal survival.

Anti-PLA_2R antibody levels have been shown to decline in response to immunosuppressive therapy. In an observational study, high-risk patients receiving oral cyclophosphamide or mycophenolate mofetil in combination with corticosteroids had a rapid decline in anti-PLA_2R antibodies following treatment [38]. Baseline antibody levels did not predict response to treatment but patients who were antibody-negative 5 years following treatment were more likely remain in persistent remission [38]. In another prospective study of 101 patients who received immunosuppression, antibody levels fell by 69–81% (depending on the assay) and proteinuria fell by 38.8% within 3 months [39]. The decline in proteinuria continued up until 12 months, whereas antibody levels remained within low range.

A prospective trial showed that patients treated with rituximab who showed an immunologic response were more likely to achieve remission [40]. The decline in anti-PLA_2R antibodies preceded the corresponding reduction in proteinuria, which may allow response to rituximab to be predicted and subsequent dosing to be determined. In another prospective trial of patients with persistent nephrotic syndrome treated with rituximab, lower antibody titers at baseline and full antibody depletion at 6 months following rituximab treatment strongly predicted remission (HR 7.90, 95% CI 2.54–24.60, $P < 0.001$) [41]. Similarly, in each case of CR ($n = 25$), antibody depletion preceded clinical remission. On average, a 50% reduction in antibody titer preceded a 50% reduction in proteinuria by 10 months.

Treatment

We can rationally assign patients to nonimmunosuppressive therapy or to immunosuppressive therapy according to their risk for renal disease progression. Table 16.1 summarizes GRADE recommendations for the treatment of membranous nephropathy.

Nonimmunosuppressive Therapy

Nonimmunosuppressive therapy is based on controlling edema, dietary protein intake, blood pressure, and hyperlipidemia. Interventions are indicated based on evidence available in adults with proteinuria renal disease.

Blood Pressure

In patients with proteinuric renal disease, including membranous nephropathy, there is high certainty evidence that the target for blood pressure is ≤125/75 mmHg [42]. Angiotensin-converting enzyme inhibitor (ACEi) and/or angiotensin receptor blockers (ARBs) are effective antihypertensive agents that can reduce proteinuria and slow progression of renal disease in both diabetic and nondiabetic chronic nephropathy patients, and for these reasons they are the preferred agents to treat hypertension in proteinuric renal diseases. In the Modification of Diet in Renal Disease study, patients with proteinuria of >1 g/day had a significantly better outcome if their blood pressure was reduced to 125/75 mmHg [43].

Patients need to be instructed to follow a low-salt diet because high salt intake (e.g. 200 mg Na or 4.6 g sodium/day) can significantly impair the beneficial effects of angiotensin II blockade [44].

Lipid Lowering

Statins may have a synergistic antiproteinuric effect when combined with ACEi, but this effect is small and mainly observed in patients with proteinuria of <3 g/24 h. When used in combination with high-dose cyclosporine (CsA), statins may increase the risk of rhabdomyolysis [45].

Thromboembolism Prophylaxis

Prophylactic anticoagulation has been shown in retrospective reviews to be beneficial in reducing fatal thromboembolic episodes in nephrotic patients with membranous nephropathy without a concomitant increase in the risk of bleeding [46]. In general, membranous nephropathy patients who are severely nephrotic (proteinuria of >10 g/day and serum albumin of <2.5 g/dl) are candidates for anticoagulation.

Immunosuppressive Therapy

Several treatment strategies, including a variety of immunosuppressive agents, have been shown to be at least partially successful in reducing proteinuria in membranous nephropathy [47]. The available evidence is presented according to the risk group (e.g. low, medium, and high) that the patients in the studies most closely represent. Table 16.2 summarizes the different risk groups.

Treatment of Low-risk Patients

Evidence to support this approach comes from published validation studies and from data on the clinical relevance of PR [37, 48]. Treatment should be nonimmunosuppressive therapy only, given the excellent prognosis of this group of patients when untreated.

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Table 16.1 GRADE recommendations for treatment of membranous nephropathy.

Treatment	Recommendation	Certainty of evidence	Strength of recommendation
Blood pressure lowering	We recommend using ACEi or ARB to achieve a target blood pressure of ≤125/75 mmHg. ACEi or ARB also help to reduce proteinuria and slow the progression of kidney disease.	Moderate–high	Strong
Low-salt diet	We suggest a low-salt diet because high salt intake (e.g. 200 mg Na or 4.6 g sodium/day) can significantly impair the beneficial effects of angiotensin II blockade	Low	Weak
Lipid-lowering therapy	Statins combined with ACEi have synergistic effect in reducing proteinuria	Low	Weak
Thromboembolism prophylaxis	We suggest prophylactic anticoagulation in patients with proteinuria ≥10 g/day and serum albumin below 2.5 g/dl as they are at high risk of fatal thromboembolism	Low	Weak
Nonimmunosuppressive therapy	We suggest initial treatment with nonimmunosuppressive therapy comprising of ACEi or ARB, low-salt diet and statins for 6 months before starting immunosuppressive therapy. However, patients with high-risk of progression will need to start immunosuppressive therapy earlier.	Moderate	Strong
Cytotoxics and corticosteroids	We recommend a 6-month course of corticosteroids with oral cytotoxic agent as first-line therapy	High	Strong
Calcineurin inhibitor with or without corticosteroids	We recommend calcineurin inhibitor as first-line therapy or for patients who cannot tolerate cytotoxic agents. There is high risk of relapse once calcineurin inhibitors are ceased hence might need long-term treatment with calcineurin inhibitor.	High	Strong
Mycophenolate mofetil with or without corticosteroids	We suggest mycophenolate mofetil with corticosteroids in patients refractory to other agents. There is high risk of relapse.	Low	Weak
Rituximab	We suggest rituximab as first-line therapy or for patients with refractory disease	Low	Weak

Table 16.2 Risk assessment for progressive decline in kidney function.

Low risk	Medium risk	High risk
Patients in the low-risk group are categorized by a <5% risk for progression over 5 years of observation They are defined by normal renal function and proteinuria of ≤4 g/24 h over a 6-month observation period	Patients in the medium-risk group are defined by normal renal function and persistent proteinuria between 4 and 8 g/24 h over 6 months of observation despite the institution of maximum conservative therapy	Patients in the high-risk group are characterized by progressive loss of renal function and/or by persistent high-grade proteinuria of ≥8 g/24 h during the 6 months of observation

Treatment of Medium-risk Patients

Patients in this group should be treated with nonimmunosuppressive treatment for at least 6 months before being considered for immunosuppressive therapy.

Corticosteroids Corticosteroid therapy alone may provide little or no benefit for induction of remission or preservation of kidney function even after the data are adjusted to include only patients with proteinuria at entry of >3.5 g/24 h (Table 16.3).

Cytotoxic Agents Combined with Corticosteroids Cyclophosphamide and chlorambucil in combination with corticosteroids appear to be effective in the treatment of patients with idiopathic membranous nephropathy and preserved renal function, with benefits maintained well beyond the 1-year treatment period, although relapse rates approached 35% at 2 years. The long-term adverse effects of these cytotoxic agents, in particular, effects on fertility and also malignancy are the major drawbacks to the universal application of this form of therapy. The risk of malignancy is not increased for patients treated with cumulative cyclophosphamide doses of ≤36 g but increases significantly in patients with cumulative cyclophosphamide doses of ≥36 g [53]. These studies are summarized in Table 16.4 [8, 54–69].

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Table 16.3 Corticosteroid treatment in idiopathic membranous nephropathy.

Author	Year	Type of study	Risk group	n	Treatment regimens	Follow-up (months)	Outcomes/comments
Collaborative Study of the Adult Idiopathic Nephrotic Sydrome (CSAINS) [49]	1979	RCT	Medium	72	Prednisone 100–150 mg PO on alternate days × 8–12 weeks vs. placebo	23	10 of 38 controls, but only 1 of 34 given prednisone had SCr > 5 mg/dl or died Rapid decline of renal function in controls considered unexpected
Cattran [50]	1989	RCT	Medium	158	Prednisone 125–150 mg PO on alternate days × 6 months vs. placebo	48	Proportion of patients with CR similar in the two groups No differences in annual change in CrCl between the two groups No sustained difference in proteinuria
Cameron [51]	1990	RCT	High	107	Prednisolone 45 mg/m^2 on alternate days × 8 weeks vs. placebo	52	No difference in remission rates for NS in either short (6 and 12 months) or long (48 months) term No differences in rates of renal function decline
Short [52]	1987	Prospective nonrandomized study	High	15	MTP 1 g IV × 5 days followed by prednisolone 100 mg, 75 mg 50 mg, then 25 mg on alternate days for 4 weeks, then dose decreasing by a further 5 mg each month	32	Serum creatinine fell by a mean of 46% In 10 patients the beneficial effect was sustained, but in three it had reversed by 6 months In the other two patients the progressive decline of renal function was not influenced

CR, complete remission; CrCl, creatinine clearance; IV, intravenous; MTP, methylprednisolone; NS, nephrotic syndrome; PO, per oral; RCT, randomized controlled trial; SCr, serum creatinine.

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Table 16.4 Cytotoxic treatment in idiopathic membranous nephropathy.

Author	Year	Type of study	Risk group	*n*	Treatment regimens	Mean Follow-up (months)	Outcomes/comments
Ponticelli [54]	1984	RCT	Medium	67	MTP 1 g IV × 3 days followed by MTP 0.4 mg/kg PO × 27 days, on months 1, 3, and 5 and CHL (0.2 mg/kg/day) on months 2, 4, and 6 vs. symptomatic therapy	31	At the end of follow-up 23 of 32 treated patients (72%) were in CR or PR, as compared with 9 out of 30 controls (30%).
Ponticelli [55]	1992	RCT	Medium	92	MTP 1 g IV × 3 days followed by MTP 0.4 mg/kg PO × 27 days on months 1, 3, and 5 and CHL (0.2 mg/kg/day) on months 2, 4, and 6 vs. MTP alone	48	At 3 years, 66% remission in MTP/CHL group vs. 40% in MTP group. At 4 years, the difference was no longer statistically significant.
Ponticelli [56]	1995	RCT	Medium	67	MTP 1 g IV × 3 days followed by prednisone 0.5 mg/kg/day × 27 days on months 1, 3, and 5 and CHL (0.2 mg/kg/day) on months 2, 4, and 6 vs. symptomatic therapy	120	92% probability of renal survival in treated compared with 60% in the control group. 8% of treated patients vs. 40% of the untreated group reached ESRD.
Ponticelli [57]	1998	RCT	Medium	87	MTP 1 g IV × 3 days followed by MTP 0.4 mg/kg/day PO × 27 days on months 1, 3, and 5 alternating with either CHL 0.2 mg/kg/day or CYC 2.5 mg/kg/day on months 2, 4, and 6	36	CR/PR in 82% of patients on MTP/CHL vs. 93% on MTP/CYC (P = NS). Side effects lower in the MTP/CYC group.
Jha [58]	2007	RCT	Medium	93	MTP 1 g IV × 3 days followed by prednisolone 0.5 mg/kg/day PO × 27 day on months 1, 3, and 5 and CYC 2 mg/kg/day on months 2, 4, and 6 vs. conservative therapy	120	CR/PR in 72% of patients on MTP/CYC vs. 35% in control group
Murphy [59]	1992	RCT	Medium	40	CYC 1.5 mg/kg × 6 months + DIP/W24 × 2 years vs. symptomatic therapy		Treatment group had less proteinuria. No differences in renal function at 2 years
Donadio [60]	1974	RCT	Medium	22	CYC 1.5–2.5 mg/kg PO × 1 year vs. symptomatic therapy	12	No benefit of CYC on proteinuria, renal function, or histology
Falk [61]	1992	RCT	High	26	Prednisone 2 mg/kg on alternate days × 8 weeks, tapered over 4 weeks, vs. CYC 0.5–1 g/m^2 IV monthly × 6 months + MTP (7 mg/kg) × 3 followed by prednisone (2 mg/kg/alternate days) for 8 weeks, then tapered over next 4 weeks	29	No impact of CYC on renal function, level of proteinuria, or progression to ESRD
West [62]	1987	Case-control study	High	26	CYC 2 mg/kg × 20 ± 4 months ± prednisone vs. prednisone or symptomatic therapy	49	CYC associated with an increased rate of remission of NS and better preservation of renal function. Adverse effects were significant.
Jindal [63]	1992	Case-control study	High	9	CYC (1–2 mg/kg/day) for a mean of 23 ± 4 months (8–54) ± prednisone (6/9 patients; dose 33 ± 9 mg/day) compared to 17 controls receiving prednisone, maximum dose 50–125 mg alternate days in 9/17 and 40–80 mg in 6/17, for a mean of 20 ± 4 months	64–83	CR in 4/9 and PR in 5/9 in CYC group. One patient in the CYC group and 10 patients in control group reached ESRD. Four relapses in 3 treated patients, and 3 of 4 responded to repeat therapy. Of the 7 controls who did not reach ESRD, only 2 had persistent NS.

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Torres [64]	2002	Case-control study	High	19	Prednisone (1 mg/kg/day month 1, 0.5 mg/kg/day month 2, 0.5 mg/kg/day months 3–6) together with CHL 0.15 mg/kg/day for the first 14 weeks vs. historic control group on symptomatic therapy	48	At the end of follow-up, 65% of patients in the control group had reached ESRD, 10% had advanced renal failure, and 25% had died. Majority of treated patients showed stabilization or improvement of renal function.
Bruns [65]	1991	Prospective nonrandomized	High	11	CYC, 100 mg/day in all patients + prednisone (60–100 mg alternate days) in 10/11 patients for 1 year	24–25	Serum creatinine decreased in 10 patients on combined therapy by 6 months and remained stable in 7/8 followed long-term. Proteinuria decreased from 11.9 to 2.3 g/day. Similar course observed in the 1 patient on CYC alone.
Warwick [66]	1994	Prospective nonrandomized	High	21	Prednisolone 125 mg alternate days on months 1, 3, and 5 and CHL 10 mg/day on months 2, 4, and 6. Later patients received MTP 1 g iv × 3 at the start first cycle of treatment. Four patients were retreated.	39	Renal function stable or improved in 11/21 patients (52%). Of these 11, PR in 4 and CR in 2. Serum creatinine > 5.7 mg/dl or ESRD in 6 patients (29%). 3 patients died. Side effects + significant complications related to therapy in > 50% of patients.
Branten [67]	1998	Prospective nonrandomized	High	32	MTP 1 g IV × 3 days, followed by prednisone (0.5 mg/kg/day months 1, 3, and 5) and CHL (0.15 mg/kg/day months 2, 4, and 6), or CYC (1.5–2 mg/kg/day for 1 year) + steroids in a comparable dose	26–38	Renal function improved in both groups but the improvement was short-lived in the CHL group. Remissions of proteinuria more frequent after CYC treatment (15/17 vs. 5/15). CHL associated with more side effects.
Du Buf-Vereijken [68]	2004	Prospective nonrandomized	High	65	MTP 1 g IV × 3 days at months 1, 3, and 5, and prednisone 0.5 mg/kg/48 h for 6 months + CYC (1.5–2 mg/kg/day) × 12 months	51	Renal function improved or stabilized in all patients. At the end of follow-up, CR in 16, PR in 31, 4 progressed to ESRD, and 5 patients had died. Overall survival 86% after 5 years.
Mathieson [69]	1988	Prospective nonrandomized	High	8	MTP 1 g IV × 3 days, 0.5 mg/kg/day PO × 27 days, then CHL 0.15–0.2 mg/kg × 28 days × 3 cycles	8	Renal function improved in 6, stabilized in 1, and deteriorated in 1 patient. Proteinuria fell from 15 to 2 g/day. Side effects were severe.

CHL, chlorambucil; CR, complete remission; CYC, cyclophosphamide; DIP/W, dipyridamole/warfarin; IV, intravenous; MTP, methylprednisolone; PO, per oral; PR, partial remission; RCT, randomized controlled trial.

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Cyclosporine A CsA can induce a remission (CR or PR) of NS in 50–60% of patients. Prolonged low-dose CsA (~1.5 mg/kg/day) could be considered for long-term maintenance of patients who achieve CR or PR, especially in patients at high risk for relapse [70]. It is important to emphasize that although reduction of proteinuria usually occurs within a few weeks, the majority of CR occurred after more than 6 months of treatment. On the other hand, if after 3–4 months of CsA therapy at adequate doses proteinuria is not significantly reduced, it is unlikely that the therapy will be effective. These studies are summarized in Table 16.5 [72–76].

Tacrolimus Similar to patients treated with CsA, maintenance of remission may require prolonged use of low-dose tacrolimus (TAC). In a single randomized controlled trial in 25 patients with normal kidney function and nephrotic range proteinuria, tacrolimus monotherapy incurred complete remission in 94% of patients prescribed tacrolimus compared to 35% in the control group [77]. A small number of patients (six patients in the control group and one in the TAC group) reached the secondary end point of a 50% increase in serum creatinine, resulting in low certainty evidence for this outcome.

Treatment of High-risk Patients

Corticosteroids

Randomized, controlled trial evidence is available in a small number of patients with high-risk disease. Based on low certainty evidence, corticosteroid therapy alone may offer little or no benefit for preserving kidney function or lowering proteinuria (Table 16.3) [49–52].

Cytotoxic Agents Combined with Corticosteroids Prednisolone combined with chlorambucil may retard progression of kidney failure compared to steroid therapy and supportive treatment alone [78]. The addition of CsA to steroid therapy is likely to have similar clinical effects compared to chlorambucil, although may incur fewer serious adverse events.

A summary of the studies conducted in this group of patients is presented in Table 16.4 [54–69].

Cyclosporine There has been only one controlled trial with 17 participants evaluating CsA in patients with high-grade proteinuria and progressive renal failure [72]. CsA was associated with significant reduction in proteinuria and prevented loss (slope) of renal function [70–75]. A summary of studies is presented in Table 16.5.

Mycophenolate Mofetil There has been a paucity of studies using mycophenolate mofetil for membranous nephropathy leading to low or very low certainty evidence. Current evidence for mycophenolate mofetil is based on nonrandomized studies (Table 16.6) [79–81]. Based on low certainty evidence from uncontrolled studies, mycophenolate mofetil has uncertain benefits in high-risk membranous nephropathy. Based on a study including historical controls treated with cyclophosphamide, relapses may occur more frequently with mycophenolate mofetil therapy [81].

Rituximab Rituximab is a chimeric monoclonal antibody against CD20+ B cells and as membranous nephropathy is an autoimmune disease, rituximab has been studied in the treatment of patients with membranous nephropathy. Prospective uncontrolled studies have been performed evaluating the efficacy of rituximab in idiopathic membranous nephropathy and are summarized in Table 16.7. These studies have led to the hypothesis that rituximab may modify disease progression in membranous nephropathy.

Two randomized controlled studies provide evidence for rituximab in membranous nephropathy. In the small (75 participants) Evaluate Rituximab Treatment for Idiopathic Membranous Nephropathy (GEMRITUX) study, rituximab (375 mg/m^2 on days 1 and 8) may have induced a higher rate of disease remission during extended follow-up (up to 18 months) compared to standard therapy alone [82].

The Membranous Nephropathy Trial Of Rituximab (MENTOR) study (NCT01180036) is a multicenter randomized controlled trial in 126 participants comparing the efficacy and safety of rituximab to CsA in medium- to high-risk patients with idiopathic membranous nephropathy [91]. Patients with proteinuria ≥5 g/day following a minimum of 3 months conservative nonimmunosuppressive therapy were randomized to receive IV rituximab (days 1 and 15, then repeated at 6 months) or oral CsA (3.5 mg/kg/day for 12 months). Based on results in a conference proceeding, participants who received rituximab more frequently achieved CR or PR (odds ratio 6.0, 95% CI 2.7–13.2).

Table 16.7 summarizes the studies using rituximab in membranous nephropathy [41, 82–92]. Together these studies suggest rituximab could be considered as first-line treatment for membranous nephropathy, but we need larger trials with hard endpoints such as ESKD to change our current practice. Most importantly, so far there is no published study comparing rituximab with the current first-line therapy, i.e. combination of cytotoxics and corticosteroids.

Eculizumab Eculizumab is a humanized anti-C5 monoclonal antibody designed to prevent the cleavage of C5 into its proinflammatory by-products. In a randomized

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Table 16.5 Cyclosporin A treatment in idiopathic membranous nephropathy.

Author	Year	Type of study	Risk group	*n*	Treatment regimens	Follow-up (months)	Outcomes/comments
Cattran [71]	2001	RCT	Medium	51	Prednisone (0.15 mg/kg/day) plus CsA (3–4 mg/kg/day) vs. placebo plus prednisone × 26 weeks.	19.5	75% of patients in CsA group vs. 22% in control group achieved PR or CR. Relapse rate 43% in CsA group vs. 40% in placebo by week 52.
Cattran [72]	1995	RCT	High	17	CsA 3.5 mg/kg/day × 12 months vs. placebo	21	CsA associated with slower rate of decline in renal function. Sustained remission of proteinuria in 6/8 CsA patients.
Alexopoulos [70]	2006	RCT	Medium	51	CsA 2–3 mg/kg/day and prednisone vs. CsA (same dose) alone for 12 months. Responders were placed on long-term low-dose CsA 1–1.5 mg/kg/day and prednisone vs. CsA alone.	26	After 12 months of treatment, 26 patients in the combination group and 17 patients in the CsA alone group had a CR or PR of proteinuria. Daily CsA dose was higher in nonrelapsers in both groups while relapsers in both groups had lower CsA trough levels
Ambalavanan [73]	1996	Prospective nonrandomized	Medium	41	CsA 4–5 mg/kg/day for 3–6 months. Lupus serology (+) in 12 patients. Retreatment in 20 of 31 patients who relapsed after stopping CsA.	18	CsA lowered median proteinuria by 56% from 7.3 to 3.2 g/24 h. In 6 patients with declining GFR during prolonged CsA therapy, a repeat biopsy showed more prominent immune deposits and thicker GBM.
Rostoker [74]	1993	Prospective nonrandomized	High	15	CsA 4–5 mg/kg × 12–30 months prednisone 1–2 mg/kg/day × 2 months	40	CR or PR in 11/15 (73%) patients. Relapse in 3/9 on CsA withdrawal, but the relapse remain sensitive to CsA. All patients had received corticosteroids (1 mg/kg/day × 2 months) prior to enrollment.
DeSanto [75]	1987	Case series	Medium-Low	5	CsA 7 mg/kg/day for 6 months plus MTP 1–0.3 mg/kg/day for 1 month, reduced to 0.3–0.15 mg/kg on the second month, and then down to 0.15 mg/kg for 4 months	8	All had failed prior cytotoxic therapy. Prompt remission of proteinuria in 4/5 patients. No renal failure.

CR, complete remission; CsA, cyclosporin A; GBM, glomerular basement membrane; MTP, methylprednisolone; PR, partial remission; RCT, randomized controlled trial.

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Table 16.6 Mycophonolate mofetil in medium- to high-risk idiopathic membranous nephropathy.

Author	Year	Type of study	Risk group	*n*	Treatment regimens	Median Follow-up	Outcomes
Miller [79]	2000	Retrospective study	Medium–high	16	Mycophenolate mofetil 500–2000 mg/day for 8 months	8 months	6 patients had a ≥50% reduction in their proteinuria, 2 had a minor reduction in proteinuria, 4 had no change, 3 withdrew because of significant adverse effects, and 1 stopped treatment. There were no significant changes in mean serum creatinine, or serum albumin levels.
Choi [80]	2000	Retrospective study	Medium–high	15	Mycophenolate mofetil 500–1000 mg twice daily for a mean of 12 months combined with steroids	12 months	There was 61% reduction of proteinuria (7.8 to 2.3 g/24 h; $P = 0.001$), with 8 patients having PR and 2 patients CR. Renal function improved in 3 of 6 patients with kidney failure.
Branten [81]	2007	Clinical trial with historic controls.	Medium–high	32	Mycophenolate mofetil 1000 mg twice a day for 12 months (intervention). Cyclophosphamide, 1.5 mg/kg/day for 12 months (historical control). Both groups also received methylpredisone IV 1 g three times at months 1, 3, and 5, followed by oral predisone at 0.5 mg/kg every other day for 6 months, with subsequent tapering.	12 mo	Cumulative incidences of remission of proteinuria at 12 months were 66% in the mycophenolate mofetil group vs. 72% in the cyclophosphamide group ($P = 0.3$). There were more relapses in mycophenolate mofetil-treated group.

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Table 16.7 Rituximab treatment in idiopathic membranous nephropathy.

Author	Year	Type of study	Risk group	*n*	Treatment regimens	Median Follow-up (months)	Outcomes/comments
Dahan [82]	2017	RCT	Medium–high	75	RTX 375 mg/m^2 on day 1 and 8 + NIAT vs. NIAT alone	17.0	At 6 months, 13 of 37 (35.1%) treated with RTX + NIAT achieved remission vs. 8 of 38 (21.1%) controls ($P = 0.21$). Significantly higher rates of PLA_2R antibody depletion at 3 and 6 months in RTX + NIAT group.
Fiorentino [83]	2016	Prospective nonrandomized	Medium–high	38	RTX 375 mg/m^2 monthly × 6	15	29 of 38 (76.3%) achieved remission: 15 (39.5%) CR and 14 (36.8%) PR. Proteinuria significantly reduced. Renal function stable. No significant adverse events.
Bagchi [84]	2018	Retrospective	High	21	RTX 500 mg × 2 doses 7–10 days apart ± 3rd dose after 4–6 weeks if CD19 not depleted	13	13 of 21 (61.9%) achieved remission: 4 (19.05) CR and 9 (42.9%) PR. One patient relapsed after achieving PR. Renal survival was significantly better in responders ($P = 0.0037$).
Moroni [85]	2017	Prospective nonrandomized	Medium–-high	34	RTX 375 mg/m^2 × 1 dose ($n = 18$) or × 2 2 weeks apart ($n = 16$)	23.9 (mean)	At 12 months, 5 (14.7%) CR, 10 (29.4%) PR, and 19 (55.8%) no response. Outcome similar for one vs. two doses.
Waldman [86]	2016	Prospective nonrandomized	High	13	CsA 3 mg/kg/day for 6 months then tapered by 50 mg/day every 3 weeks plus RTX 1000 mg day 1 and 15, then after 6 months when CD19+ B cell count ≥5 cells/μl	41 (mean)	By 6 months 85% achieved remission (CR + PR). By 12 months, 54% achieved CR. 2 relapsed by 24 months. Treatment well tolerated.
Ruggenenti [41]	2015	Prospective nonrandomized	High	132	RTX 375 mg/m^2 weekly × 4	30.8	84 of 132 (63.6%) achieved remission (CR + PR), 43 (32.6%) achieved CR. Anti-PLA_2R antibody depletion preceded remission.
Ruggenenti [87]	2003	Prospective nonrandomized	Medium	8	RTX 375 mg/m^2 weekly × 4	Not specified	Significant reduction in proteinuria. Renal function stabilized. 2 achieved CR and 3 achieved PR.
Ruggenenti [88]	2012	Prospective nonrandomized	High	100	RTX 375 mg/m^2 weekly × 4	29 (median)	At end of follow-up, 65% achieved CR or PR. Median time to remission 7.1 months. Renal function improved in those who achieved CR.

(*Continued*)

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Table 16.7 (Continued)

Author	Year	Type of study	Risk group	*n*	Treatment regimens	Median Follow-up (months)	Outcomes/comments
Fervenza [89]	2010	Prospective nonrandomized	Medium	20	RTX 375 mg/m^2 weekly × 4, repeated at 6 months	Not specified	Proteinuria reduced from 11.9 g/24 h to 4.2 and 2.0 g/24 h at 12 and 24 months, respectively. At 24 months, 4 of 18 achieved CR, 12 of 18 achieved PR, and 1 relapsed. Remission rates higher than fortnightly dosing.
Fervenza [90]	2008	Prospective nonrandomized	High	14	RTX 1000 mg on days 1 and 15, repeated at 6 months if proteinuria >3 g/24 h and CD9+ B cell >15 cells/μl	12	At 6 months, 4 achieved PR. At 12 months, 2 achieved CR and 6 PR.
Fervenza [91] (results from abstract)	2015	RCT	High	130	RTX 1000 mg on days 1 and 15, repeated at 6 months vs. CsA 3.5–5 mg/kg/day for 6 months	24	At 24 months, CR or PR in RTX arm was 62.5% vs. 20.6% in the CsA arm. Treatment failure higher in CsA group compared to RTX group (79.4% vs. 37.5%).
Rojas-Rivera [92]	2015	RCT	High		MTP 1 g IV days 1–3 then MTP p.o. 0.5 mg/kg/day for days 4–30 on months 1, 3, and 5 and cyclophosphamide PO 2.0 mg/kg/day for 30 days on months 2, 4, and 6 vs. tacrolimus 0.05 mg/kg/day for 6 months, then tapered to withdrawal by 9 months + RTX 1 g at day 180.		Awaited

CR, complete remission; CsA, cyclosporine; IV, intravenous; MTP, methylprednisolone; NIAT, nonimmunosuppressive antiproteinuric therapy; PO, per oral; PR, partial remission; RCT, randomized controlled trial; RTX, rituximab.

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Table 16.8 Adrenocorticotrophic hormone treatment in idiopathic membranous nephropathy.

Author	Year	Level of Evidence	Risk Group	N	Treatment regimens	Median Follow-up	Outcomes
Berg [94]	1999	Prospective uncontrolled	Medium–high	14	ACTH 1 mg intramuscular. The dose of ACTH was increased from one injection every other week to three injections per week during a period of 8 weeks.	70 days	Urinary albumin excretion dropped from 4830 mg/day (3660–15877) to 1040 mg/day (630–3750). Serum creatinine went up from 135 μmol/l (98–314) to 110 μmol/l (98–210)
Ponticelli [96]	2006	RCT	Medium	32	Group A (16 patients) received methylprednisolone(1 g) administered IV on 3 consecutive days, and then orally 0.4 mg/kg for 27 days on months 1, 3, and 5. On months 2, 4, and 6, received either chlorambucil (0.2 mg/kg/day orally) or cyclophosphamide (2.5 mg/kg/day orally). Group B (16 patients) received tetracosactide (a synthetic analogue of ACTH), intramuscular injection of 1 mg between 7:00 and 9:00 a.m. Administration of ACTH was increased from 1 injection every other week to 2 injections per week for a total treatment period of 1 year.	22 months	CR or PR in group A was 93% (CR 5 and PR 10 patients) and 87% in group B achieved CR or PR (10 CR and 4 PR). There was no significant difference in either treatment group.
Hladunewich [97]	2014	RCT (nonblinded dose finding study)	Medium	20	Patients received either 40 or 80 units of ACTH. The dose of ACTH was increased from one injection every other week to two injections per week for total of 12 weeks	12 months	In both groups combined, the mean proteinuria improved significantly from 9.1 ± 3.4 g/day to 3.9 ± 4.2 g/day at 1 year of follow-up

ACTH, adrenocorticotrophic hormone; CR, complete remission; PR, partial remission; RCT, randomized controlled trial.

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controlled trial 200 patients with membranous nephropathy were treated every 2 weeks with two different intravenous dose regimens and compared to a placebo group over a total of 16 weeks [93]. In low certainty evidence, eculizumab did not have a detectable effect on proteinuria or renal function compared to placebo.

Adrenocorticotropic Hormone

Synthetic adrenocorticotropic hormone has been studied by various investigators as a treatment option for idiopathic membranous nephropathy [94–97]. These studies have been summarized in Table 16.8. However, these studies have small sample size with only short-term follow up. There is low-certainty evidence that adrenocorticotropic hormone has a significant effect on proteinuria.

Patients with severe renal insufficiency (serum creatinine of ≥3 mg/dl) are less likely to benefit from immunosuppression therapy, and the risk of treatment is significantly higher, so these patients should be considered for conservative therapy only and with plans made for transplantation in the future.

Disease and Treatment Summary

In conclusion, control of nephrotic syndrome, specifically with CR or PR, is strongly associated with renal survival and a slower rate of chronic kidney disease (CKD) progression. There are no standard or universal first-line specific therapeutic options for idiopathic membranous nephropathy. There is moderate to high certainty evidence that blood pressure lowering therapy aiming for a blood pressure 125/75 or below will retard CKD progression. There is low certainty evidence that statins, salt restriction, and prophylactic anticoagulation have a role in the treatment of membranous nephropathy.

In patients who are at low risk of progression, therapy focused on blood pressure lowering should suffice, although long-term follow-up is needed to ensure that there is no disease progression or worsening of proteinuria.

Patients at medium or high risk are candidates for additional immunosuppressive therapy. Patients with persistent nephrotic-range proteinuria are at increased risk for cardiovascular and thromboembolic complications. Proteinuria is an inducer of kidney injury and plays a major role in the development of progressive tubular injury, interstitial fibrosis, and subsequent loss in GFR. The higher the sustained level of proteinuria, the more likely the development of end-stage renal disease. Therefore, even if the main benefit of immunosuppressive therapy is to accelerate the induction of a remission, it may still have value in the long term. A treatment algorithm that combines the predictive factors and best evidence for immunosuppressive therapy is presented in Figure 16.1. Current first-line therapy is corticosteroids combined with cyclophosphamide or chlorambucil (which may be associated with a higher frequency of adverse events). Calcineurin

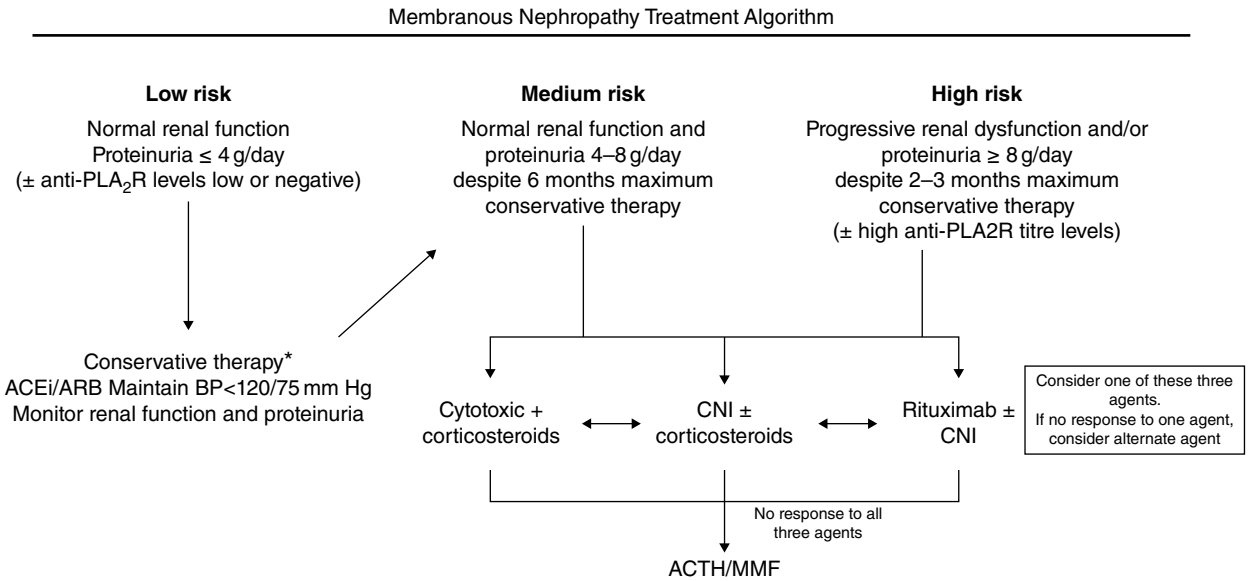

Figure 16.1 Membranous nephropathy treatment algorithm. ★Conservative treatment involves the use of ACEi ± ARB blocker to maintain blood pressure < 125/75 mmHg, lipid control with HMG-CoA reductase inhibitor, dietary protein restriction (0.6–0.8 g/kg ideal body weight/day), dietary NaCl intake (goal is 2–3 g Na) to optimize antiproteinuric effects of ACEi and ARBs, smoking cessation, and attempt to reduce obesity, if present. Abbreviations: anti-PLA_2R, phospholipase A_2 receptor antibody; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CNI, calcineurin inhibitor; ACTH, adrenocorticotrophic hormone; MMF, mycophenolate mofetil.

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inhibitors combined with low-dose prednisone may be considered for patients who prefer or are intolerant of first-line therapy. Long-term therapy may be required due to the high incidence of relapse. Emerging data suggest rituximab may provide CR or PR at 24 months. Patients who do not respond well or relapse after a first course of immunosuppression therapy may benefit from a second course of immunosuppression [98].

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17

IgA Nephropathy in Adults and Children

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Introduction

Immunoglobulin A nephropathy (IgAN) is the most common pattern of glomerulonephritis (GN) in all countries where renal biopsy is routinely practiced and is an important cause of end-stage kidney disease (ESKD) at all ages [1, 2]. IgAN is a mesangial proliferative glomerulonephritis characterized by the predominant deposition of IgA in the glomerular mesangium. The degree of histopathologic iewwwnjury is heterogeneous, and this is reflected in the varied progression and severity of clinical presentation seen in this disease [3]. Closely associated with IgAN is IgA vasculitis (IgAV) (also known as Henoch–Schönlein purpura), a small vessel systemic vasculitis characterized by small blood vessel deposition of IgA predominantly affecting the skin, joints, gut, and kidney. The nephritis of IgAV is also characterized by mesangial IgA deposition and may be histologically indistinguishable from IgAN [4].

In this chapter, we summarize the published studies according to their level of evidence and provide recommendations for the common clinical situations that confront the nephrologist treating patients with idiopathic IgAN (Figure 17.1). In each section we describe the results of therapeutic approaches to these clinical situations in adults with IgA nephropathy, followed by a pediatric perspective for which we review the results of similar therapeutic trials in children and adolescents. Some of these reports have been reviewed previously [6]. Whenever possible, the pediatric experience with each treatment will be compared with evidence-based conclusions drawn from adult studies. In this way, we will attempt to facilitate comparison between pediatric and adult recommendations for the management of patients with IgAN. Discussions of the treatment of IgAV or secondary forms of IgAN are not included in this chapter.

Epidemiology

No clinical presentation is pathognomonic of IgAN, including the archetypal young male with episodic visible hematuria following an upper respiratory tract infection. Also, although a number of abnormalities in circulating IgA and its production have been reported in IgAN patients, cohorts are heterogeneous with respect to these abnormalities, making their diagnostic utility poor [7]. Therefore, a diagnosis of IgAN currently requires a renal biopsy, which as described below also provides important prognostic information. This requirement for a renal biopsy means the true incidence and prevalence of IgAN are difficult to determine. Indeed, the prevalence of mesangial IgA deposits found at post mortem in unselected cases is surprisingly high: 4–16% [8, 9]. Reported prevalence rates for IgAN vary across the world, ranging from 5% in the Middle East [10] to 38% in Europe [11], and reaching 50% in China and Japan [12, 13]. Asian people who live in the United States have a fourfold higher incidence of IgAN compared to Caucasian Americans of European ancestry, and a sixfold higher prevalence than African-Americans while Northern Europeans with IgAN have a two to four times greater risk of progressing to end-stage renal disease (ESRD) compared to Southern Europeans [14]. There is also a disparity in gender prevalence of IgAN: in Europe and North America there is a 3 : 1 male-to-female distribution, while this ratio is 1 : 1 in East and South East Asia [15, 16].

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Pathophysiology

Recurrence of IgAN after transplantation, and also the rare cases of resolution of IgA deposits in transplanted kidneys from donors with IgAN, supports the hypothesis that mesangial IgA is derived from a pathogenic IgA fraction within the circulating pool of serum IgA [7, 17, 18]. What defines this pathogenic IgA fraction is incompletely understood, but there is evidence for the importance of low-affinity, poorly *O*-galactosylated polymeric IgA1 molecules forming circulating IgA immune complexes with a propensity for both mesangial deposition and mesangial cell activation [19, 20]. The lack of a complete understanding of the pathogenesis of IgAN has resulted in there still being no treatment known to modify mesangial deposition of IgA. Available treatment options are mostly directed at downstream immune and inflammatory events in the glomerulus and the tubulo-interstitium that may lead to renal scarring. It is therefore likely that these are generic treatments with potential benefit in other chronic glomerular diseases.

Prognosis

Adult IgAN

The natural history of IgAN has now been well defined in a number of large series with prolonged follow-up [21]. Fewer than 10% of all patients with IgAN have complete resolution of urinary abnormalities [22] and episodes of visible hematuria become less frequent with time after diagnosis, although the majority of patients will still have persistent invisible hematuria. All patients have the potential for slowly progressive chronic kidney disease leading eventually to ESRD. Approximately 25–30% of any cohort will require renal replacement therapy within 20–25 years of presentation. From the first renal symptom, on average, 1.5% of patients with IgAN have been calculated to reach ESRD per year [23], but the observed risk varies with the diagnostic approach. Centers with a low threshold for renal biopsy for patients with mild urine abnormalities, particularly those in countries where urine screening programs are established, will likely diagnose IgAN in a larger number of patients with mild disease and good prognosis (length bias) and at an earlier stage in their disease (lead-time bias), thus favorably influencing the apparent prognosis for the cohort.

Rarely, acute kidney injury can complicate preexisting IgAN, and evaluation should include a further renal biopsy unless renal function improves rapidly with supportive measures. Acute kidney injury develops by two distinct mechanisms (Figure 17.2). There may be acute, severe immune and inflammatory injury producing crescent formation, or crescentic IgA nephropathy, which may be amenable to intensive immunosuppression. Alternatively, acute kidney injury can occasionally occur with mild glomerular injury when heavy glomerular hematuria leads to tubular occlusion and/or damage by red blood cells. This is a reversible phenomenon, and recovery of renal function occurs with supportive measures.

Pediatric IgAN

Children with progressive forms of IgAN will often not develop ESRD until they are adults [24, 25]. Thus, most pediatric trials must rely on surrogate measures, as discussed in the next section. Some reports of childhood IgAN have concluded that the risk of progressive renal failure is very low [26–28], whereas others have shown that a significant number of pediatric patients with IgAN will progress to ESRD [24, 25, 29]. It has been estimated that as many as 30% will progress to ESRD in the United States [25], but for Japanese children only 11–20% are expected to progress to ESRD [24, 28, 29]. However, similar to many adult studies, predictions are based on different selection criteria for renal biopsy candidates [28, 30]. In addition, when progressive disease occurs, it is often insidious, resulting in considerable difficulty in assessing outcomes over the short term. This also presents a significant obstacle when designing clinical trials to evaluate the effect of therapeutic interventions within a feasible time period (i.e. 2–5 years).

Prognostic Factors

Many studies have identified features at presentation that mark a poor prognosis (Table 17.1) [21]: proteinuria more than 1 g/24 h, raised serum creatinine, and hypertension. The severity of proteinuria has been shown to correlate with extent of glomerular lesions [31]. In one study, 98% of patients presenting with proteinuria of <1 g/24 h had at least a 15-year renal survival [32]. Another analysis identified those with proteinuria of more than 1 g/24 h and serum creatinine more than 1.7 mg/dl. The 7-year renal survival was 99% if both values were below this threshold, 87% if either one was above the cutoff, and 21% if both were above the cutoff [33]. Episodic visible hematuria does not entail a poor prognosis. It is likely that this observation reflects the variation in time between clinical presentation and diagnosis, which can hinder the accurate interpretation of the natural history.

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Table 17.1 Prognostic markers at presentation.

Prognosis category	Clinical finding(s)	Histopathological findings
Worse prognosis	Increasing age Duration of preceding symptoms Severity of proteinuria Hypertension Renal impairment Increased body mass index Serum uric acid	*Light microscopy* Mesangial hypercellularity Endocapillary hypercellularity Segmental glomerulosclerosis Tubular atrophy/interstitial fibrosis Cellular/fibrocellular crescents *Immunofluorescence* Capillary loop IgA deposits *Ultrastructure* Capillary wall electron-dense deposits Mesangiolysis GBM abnormalities
Good prognosis	Recurrent visible hematuria	Minimal light microscopic abnormalities
No effect on prognosis	Gender Serum IgA level	Intensity of IgA deposits Codeposition of mesangial IgG, IgM, or C3

GBM, glomerular basement membrane.

The Oxford Classification of IgA Nephropathy

Renal biopsy provides important independent prognostic information about the renal outcome of patients with IgAN. The recently updated Oxford Classification of IgAN [34] identifies five morphological features that correlate strongly with clinical outcome, independent of known clinical risk factors at the time of diagnosis, including the presence of hypertension, reduced glomerular filtration rate (GFR), and degree of proteinuria as well as proteinuria and blood pressure (BP) at follow-up. These features are mesangial hypercellularity (M), endocapillary hypercellularity (E), segmental glomerulosclerosis (S), crescent formation (C), and tubular atrophy/interstitial fibrsosis (T). The presence of multiple pathological features (M, E, C, S, and/or T) in combination results in additive risk of kidney disease progression. The predictive value of these biopsy features is similar in both adults and children. Since its publication, the Oxford Classification of IgAN has been validated in different patient populations from North America, Europe, and Asia, and is now widely accepted as the histopathological scoring system of choice for IgAN [35–38].

The various prognostic factors described may be informative for groups of patients but do not have sufficient accuracy to predict the prognosis of an individual patient with complete confidence. More refined methods of assessing disease activity are required to define those patients in whom IgA deposition will lead to substantial and sustained glomerular injury. An approach incorporating information on blood pressure (BP), proteinuria, and estimated glomerular filtration rate (eGFR) at time of biopsy along with the Oxford MEST-C score has recently been developed by the International IgA Nephropathy Network (IIGANN) which allows individual risk stratification at the time of biopsy and is available at the QxMD website (https://qxmd.com/calculate/ calculator_499/international-igan-prediction-tool-adults).

Treatment

We have reviewed the English literature published on the treatment of IgAN since 1976. Despite the prevalence of IgAN, published randomized controlled trials (RCTs) are few in number, and even recent RCTs are not always sufficiently powered to provide definitive information on tested interventions. In part, this is because IgAN is a slowly progressive disease, making it necessary to study large numbers of patients for prolonged periods of time to determine the efficacy of any therapeutic intervention. Another consequence of the slowly progressive nature of IgAN is that for many of the trials now published, patient recruitment occurred at a time when the management of progressive glomerular disease was less clearly defined than it is now. These caveats are even more relevant for reports dealing with therapeutic interventions in children

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with IgAN. Although the most important outcome indicator for all patients with IgAN is based on deterioration of the GFR, the period from diagnosis to ESRD in patients with onset in childhood may be decades and may be highly heterogeneous. Thus, most studies of therapy for pediatric IgAN have relied on surrogate markers, such as deterioration in renal biopsy findings [39, 40] and/or decline in the amount of proteinuria or hematuria [40–42]. Significant deterioration in renal function (i.e. 40–50% reduction of GFR or doubling of serum creatinine concentration) is the surrogate end point most associated with progression to ESRD, although this occurs infrequently in patients participating in pediatric trials of IgAN [42].

All Patients with IgAN

Recommendations for Adults

All adult patients with IgAN should have a BP of <125/75 to 130/80 mmHg (strong recommendation, high level of evidence). The antihypertensive agents of choice should be angiotensin converting enzyme inhibitors (ACEi) and angiotensin II receptor blockers (ARB) (strong recommendation, high level of evidence). All normotensive patients with proteinuria of >1.0 g/l/1.73 m^2/day should be treated with the maximal tolerated dose of either an ACEi or ARB to reduce proteinuria as much as possible. Furthermore, all patients should have an individual assessment of their cardiovascular risk, particularly those with progressive chronic kidney disease, hypertension, and dyslipidemia, and treated accordingly (reviewed in Chapter 6).

Recommendations for Children

It is also important to maintain pediatric patients with IgAN in a normotensive range, utilizing age-, gender-, and height-appropriate norms for BP [43] (strong recommendation, high level of evidence). ACEi and ARB are the first choice for treatment of hypertension and/or proteinuria (strong recommendation, high level of evidence).

Evidence in Adults

In common with virtually all kidney diseases, hypertension is a risk factor for progression in IgAN and should be treated early in the course of the disease [21, 44]. There is, however, limited RCT evidence devoted specifically to IgAN concerning a target BP required to preserve renal function. In one 3-year RCT of 49 patients with IgAN, the

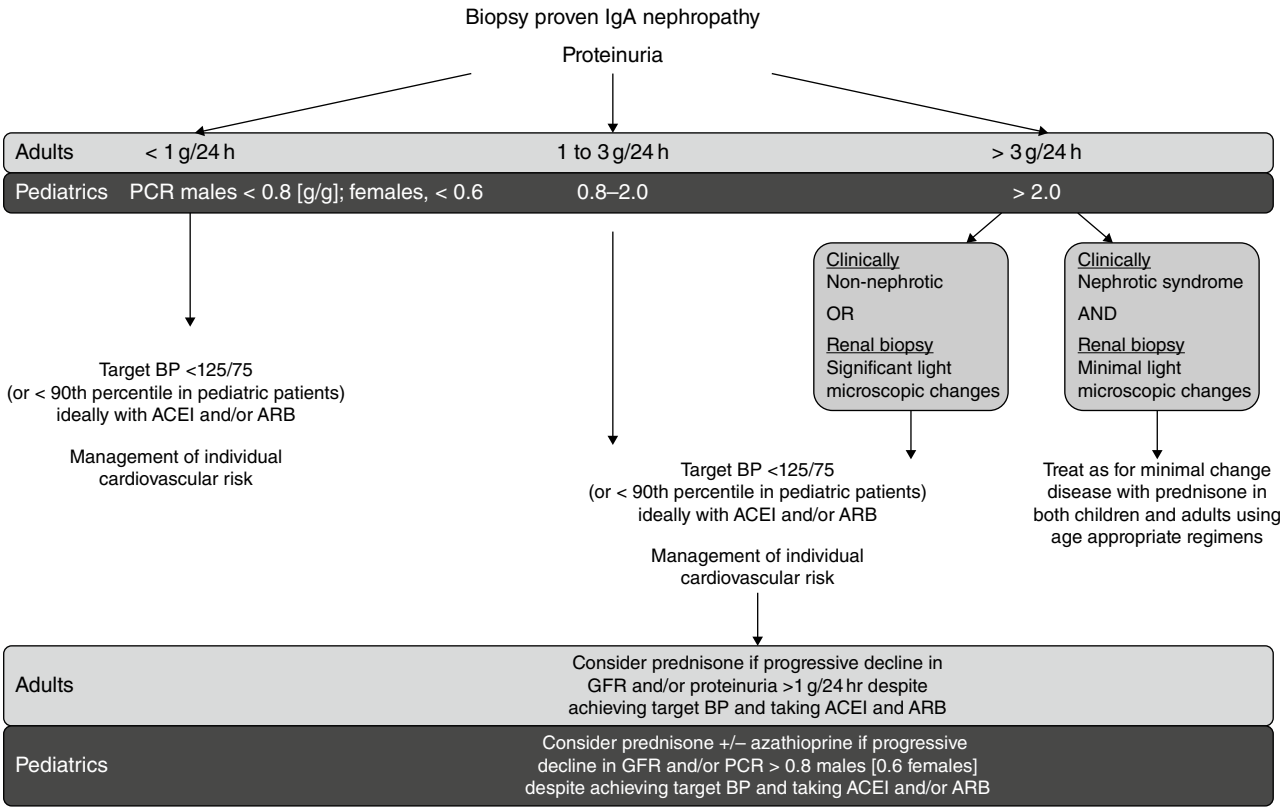

Figure 17.1 Flowchart for the management of IgA nephropathy.

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achieved mean BP of 129/70 mmHg stabilized GFR over 3 years, whereas patients with an achieved mean BP of 136/76 mmHg showed an average decline in GFR of 13 ml/min over 3 years [45]. As with other proteinuric glomerular diseases, the antiproteinuric effect of antihypertensive treatment appears to predict renoprotection, and so therapy should be titrated not only to target BP values but also to maximize reduction of proteinuria. There is increasing evidence that the antihypertensive strategy of choice should be maximal renin–angiotensin system (RAS) blockade, to both achieve a target BP of <125/75 to 130/80 mmHg and to minimize proteinuria [46] (Table 17.2). Retrospective data from the Toronto GN registry have shown that patients with IgAN treated with an ACEi to control BP had a lower rate of annual loss of renal function than similar patients treated with alternative antihypertensives [47]. This is supported by an RCT of 44 patients that demonstrated an additional benefit of an ACEi (enalapril) on progressive kidney disease in IgAN despite equivalent BP control [50]. This benefit was believed to have arisen from the additional reduction in proteinuria seen in the ACEi-treated group. Similarly, a more recent and larger RCT of 109 Asian patients showed benefit with an ARB (valsartan) both in proteinuria reduction and in retarding the rate of renal deterioration, although the investigators were unable to demonstrate a significant improvement in their primary end points of doubling of serum creatinine or ESRD at 2 years [51].

The safety of using ACEi in combination with an ARB is unclear [55, 56] and therefore should be avoided in IgAN.

Evidence in Children

A placebo-controlled RCT conducted in 23 centers in five European countries that evaluated benazepril (0.2 mg/kg/day) in 66 children and young adults <35 years of age provided evidence to support the use of ACEi in pediatric patients [54]. The patient cohort included 29 patients ≤18 years of age. Seventy-four percent of the patients had their initial renal abnormalities when they were ≤18 years old. The overall allocation of patients was 32 in the benazepril arm and 34 in the placebo arm. There was a significant benefit with benazepril in preventing progression of renal disease in these patients (defined as a reduction in GFR by 30% versus baseline or worsening of proteinuria to ≤3.5 g/l/1.73 m^2/day). Such progression was seen in 9/34 (26%) of the placebo group but only 1/32 (3%) of the benazepril group. Furthermore, at the end of the trial, the number of patients with proteinuria of <0.5 g/l/1.73 m^2/day in the benazepril group was significantly higher than the number in the placebo group (13/32 [40%] vs. 3/34 [9%]; $P = 0.0002$). This was evident in the groups of children (6/10 [60%] vs. 2/19 [10%]) and adults (7/12 [58%] vs. 1/15 [7%]) in this trial.

Patients with Recurrent Visible Hematuria

Recommendation for Adults and Children

Patients with recurrent visible hematuria require no specific additional intervention (strong recommendation, high level of evidence).

Table 17.2 Evidence for use of RAS blockade in IgAN[a].

Author [reference]	Design	*n*	Treatment	Follow-up (months)	Results
Cattran [47]	NRCT	115	ACEi	29	↑ GFR, ↓ proteinuria
Coppo [48]	NRCT	27	Captopril	26	↑ GFR, ↓ proteinuria
Maschio [49]	RCT	39	Fosinopril	9	↓ proteinuria
Kanno [45]	RCT	49	Benazapril and amlodipine	36	≈ GFR
Praga [50]	RCT	44	Enalapril	74	Slower ↓ GFR, ↓ proteinuria
Li [51]	RCT	109	Valsartan	24	slower ↓ GFR, ↓ proteinuria
Russo [52]	NRCT	8	ACEi and losartan	3	↓ proteinuria
Song [53]	NRCT	14	Ramipril and candersartan	6	↓ proteinuria
Coppo [54]	RCT	66	Benazepril	38	Slower ↓ GFR, ↓ proteinuria

GFR, glomerular filtration rate; NRCT, nonrandomized controlled trial.
[a] Overall quality of evidence is moderate: consistent effects, variable quality of design and reporting, moderate-sized and small studies, surrogate outcomes.

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Evidence in Adults

Episodes of visible hematuria are self-limiting and can be provoked by a range of mucosal, most commonly respiratory, infections. There is no evidence supporting prophylactic use of antibiotics, even in the minority of patients in whom recurrent episodes are provoked by bacterial tonsillitis. Tonsillectomy is still favored as therapy in some regions of the world, notably Japan. Although several retrospective studies of the effectiveness of tonsillectomy have been published, most contain small numbers of patients, are nonrandomized, uncontrolled trials, and have generated conflicting data. In one Japanese study tonsillectomy was shown to be an independent factor in predicting remission in 329 patients followed for a minimum of 3 years [57]. A second retrospective study from Japan looked at the outcome in 118 patients followed over 20 years, of which 48 underwent tonsillectomy [58]. Benefit from the tonsillectomy only became apparent 10 years after initial diagnosis. The concomitant use of other treatment modalities and changing therapeutic goals during the follow-up period make these data difficult to interpret. A retrospective study from Germany of 55 patients in whom 16 had a tonsillectomy suggested no benefit of tonsillectomy at 10 years [59]. A retrospective study of 112 Chinese patients, of whom 54 underwent tonsillectomy, similarly showed no difference in renal survival at 130 months [60]. The only prospective RCT of tonsillectomy combined with steroids versus steroids alone has reported 12-month outcome data and while there was a small improvement in hematuria and proteinuria in the tonsillectomy group there was no difference in the rate of eGFR decline between the groups [61].

Evidence in Children

As for adults, there are no prospective clinical trials evaluating the role of tonsillectomy in children with IgAN. In 1996, Tomioka et al. reported that 13 of 15 children with IgAN who underwent tonsillectomy had improved urinalyses, with six of them going into remission [62]. More recently, changes in the levels of hematuria and proteinuria were assessed by Sanai et al. in eight children treated with "medication" combined with tonsillectomy compared to seven "control" children treated with "medication" [63]. These patients were a small subset of a larger patient cohort (ages 3–13 years) that included five children with Henoch–Schonlein purpura nephritis and eight with "other" types of glomerulonephritis. No details were given regarding the "medication" that was employed. The authors reported that both proteinuria and hematuria improved in five of eight patients in the tonsillectomy group compared to only one of the seven children with IgAN who received medication only. However, it is of interest that significant improvement also followed tonsillectomy in five of the eight children with other glomerulonephritis.

These limited data on the effect of tonsillectomy in children with IgAN are similar to the reports in adults. Most of the studies that have been reported in both groups are retrospective in nature, are based on unvalidated surrogate markers for outcome, and are confounded by co-interventions. There is no convincing evidence that tonsillectomy will prevent progressive renal disease in children or adults, and so this procedure should not be done (weak recommendation, low level of evidence).

Patients with Isolated Invisible Hematuria and Proteinuria of <1 g/24 h

Recommendation for Adults and Children

Adult patients with isolated invisible hematuria and proteinuria of <1 g/24 h require no specific additional intervention (strong recommendation). There are insufficient data to establish a specific evidence-based recommendation for children in this category, but we suggest that such patients require no additional therapy if their urinary protein (grams)/creatinine (grams) ratio is <0.6 (boys) or <0.8 (girls) (strong recommendation, high level of evidence).

Evidence

Available data suggest that most patients presenting with proteinuria of <1 g/24 h have at least a 15-year renal survival [32]. It is generally accepted that these patients require no additional treatment, although they should receive regular follow-up. It is, however, important to note that while a threshold for proteinuria of 1 g/24 h is commonly used to identify those at increased risk of progression (and therefore warranting treatment), this is an arbitrary value and the risk attributable to proteinuria is almost certainly a continuum. Interventions that may lower proteinuria further, and are therefore likely renoprotective, for example RAS blockade, have not been tested in this setting in either adults or children.

Patients with Rapidly Declining GFR

Recommendation for Adults

Unexplained acute kidney injury complicating preexistent IgAN requires evaluation with a kidney biopsy (Figure 17.2). Crescentic IgAN associated with active

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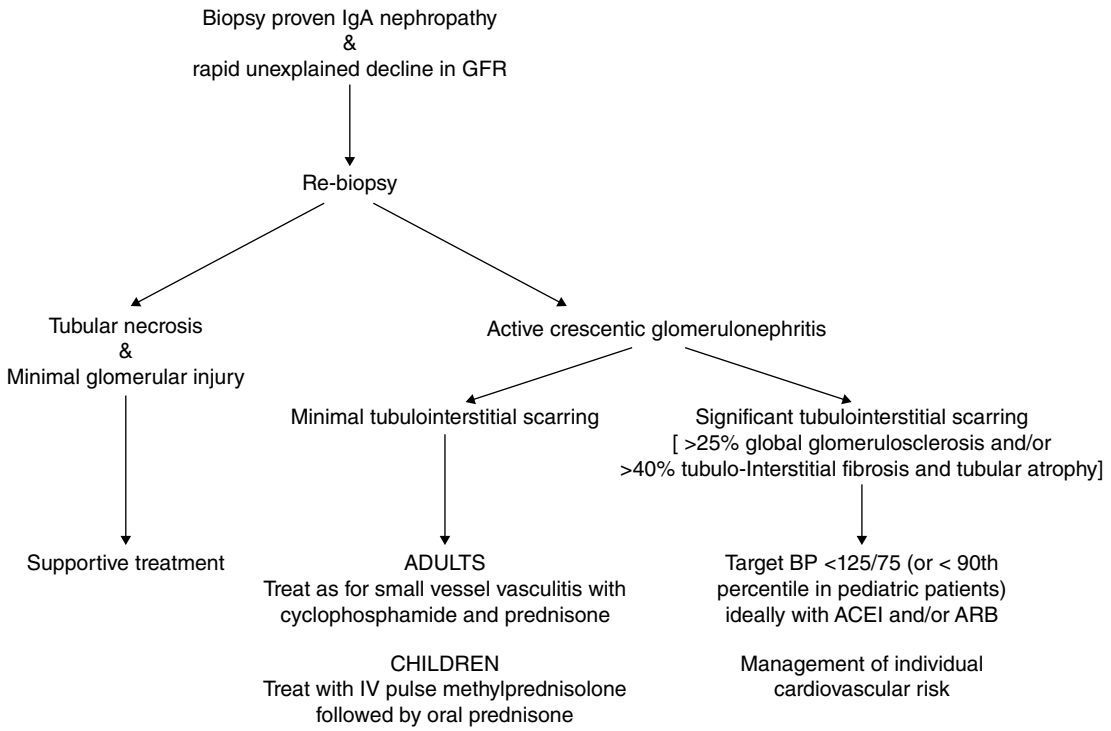

Figure 17.2 Flowchart for the evaluation and management of patients with previously diagnosed IgA nephropathy who present with a rapid unexplained decline in renal function.

glomerular inflammation and deteriorating renal function in the absence of significant chronic damage should be treated with induction therapy comprising cyclophosphamide and corticosteroids followed by maintenance therapy of azathioprine and corticosteroids at doses similar to those used for the treatment of anti-neutrophil cytoplasmic antibody-positive (ANCA) small vessel vasculitis (weak recommendation, very low level of evidence).

Recommendation for Children

Although there are no controlled trials of treatment regimens for children with crescentic IgAN, we recommend that pediatric patients with rapidly progressive disease and crescents in ≥50% of their glomeruli be treated with a 2-week course of intravenous (IV) methylprednisone pulses (six doses of 1 g/1.73 m^2 every other day), followed by 1 month of daily prednisone (1 mg/kg/day) and then alternate-day prednisone for 2–3 months (weak recommendation, very low level of evidence). Additional therapy with cyclophosphamide should be considered in patients who fail to respond to the pulse therapy (weak recommendation, very low level of evidence).

Evidence in Adults

Acute kidney injury may occur as the first presentation of IgAN with little preceding renal insult or may be superimposed on a background of preexistent disease with variable degrees of chronic glomerular and tubulo-interstitial scarring. Even if the diagnosis of IgAN has previously been established, evaluation should include renal biopsy to distinguish between acute kidney injury due to acute tubular necrosis, which should be self-limiting with supportive treatment, and crescentic IgAN, which may be amenable to intensive immunosuppression.

Crescentic IgAN has a less favorable prognosis, even with immunosuppressive therapy, than other forms of crescentic glomerulonephritis, such as ANCA-associated small vessel vasculitis; cumulative published cases suggest that renal survival in crescentic IgAN is only 50% at 1 year and 20% at 5 years [21, 64]. Evidence of chronic glomerular and tubulo-interstitial injury with scarring usually predicts a poor response to intensive immunosuppression. There is no published systematic definition of the degree of chronicity that predicts poor response to immunosuppressive treatment, but we do not recommend such an approach if a representative renal biopsy shows >40% tubulo-interstitial fibrosis and/or >25% global glomerulosclerosis.

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Table 17.3 Evidence for management of crescentic IgAN with acute kidney injury[a].

Author [reference]	Design	*n*	Treatment	Follow-up (months)	Results
Lai [65]	NRCT	2	Plasma exchange	12	Unsustained slower ↓ GFR
Nicholls [66]	NRCT	13	Plasma exchange		Unsustained slower ↓ GFR
Roccatello [67]	NRCT	9	Plasma exchange, CP and steroids	60	Unsustained slower ↓ GFR
Roccatello [68]	NRCT	20	CP and steroids	60	Slower ↓ GFR
McIntyre [69]	NRCT	9	CP and steroids	17	↑ GFR, ↓ proteinuria
Tumlin [70]	NRCT	24	CP and steroids	36	Stabilized GFR, ↓ proteinuria

CP, cyclophosphamide; GFR, glomerular filtration rate; NRCT, nonrandomized controlled trial.
[a] Overall quality very low: inconsistent effects, nonrandomized, very small studies, surrogate outcomes.

A number of case series have been published that indicate good preservation of renal function when using treatment regimens similar to those recommended for renal vasculitis, usually with high-dose corticosteroids and cyclophosphamide, and in some cases plasma exchange (Table 17.3). However, all of these series are small nonrandomized studies, most using historical controls. There has still been no RCT of these treatments in crescentic IgAN, and response to treatment is not uniform. In addition, comparisons across studies are difficult because published reports use varying definitions of crescentic IgAN. Some include cases where crescents are seen, but others include acute injury where the glomerular tuft is not intense and renal function is not deteriorating. One report indicated that there is a subset of crescentic IgAN with circulating ANCA antibodies which respond well to immunosuppression [71].

Evidence in Children

As in adults, the prognosis for children with crescentic IgAN is also poor according to most reports [72]. However, in the largest pediatric experience reported to date, Niaudet et al. described a very aggressive and successful approach to 12 children aged 8–14 years with crescentic IgAN, 10 of whom had crescents in ≥50% of their glomeruli [73]. The patients received IV methylprednisone in a dose of 1 g/1.73 m^2 every other day, followed by 1 month of daily prednisone (1 mg/kg/day) and then alternate-day prednisone for 2–3 months. Three of the patients received a second course of pulse methylprednisone, whereas three others received cyclophosphamide. Although uncontrolled, the authors described very good results after a follow-up period of 1–9 years because none of the children progressed to ESRD, nine had improved histology on repeat biopsy, and six had recovered clinically, although one patient was still hypertensive.

Patients with Nephrotic Syndrome

Recommendation for Adults and Children

In patients presenting with nephrotic syndrome, preserved renal function, and minimal glomerular injury evident on light microscopy, a trial of high-dose corticosteroids using a regimen appropriate for minimal change disease in IgAN should be considered (strong recommendation, very low level of evidence). However, there is no evidence to support prolonged exposure to corticosteroids if there is not a prompt response, nor for their use in nephrotic syndrome in the presence of structural glomerular damage.

Evidence in Adults

In many patients with IgAN, nephrotic syndrome-range proteinuria is a manifestation of significant structural glomerular damage and progressive renal dysfunction. However, a small minority of both adults and children have nephrosis with minimal glomerular change on renal biopsy, although there are also IgA deposits, and proteinuria remits promptly in response to corticosteroids. In these patients, two common glomerular diseases may coincide: minimal change nephrotic syndrome and IgAN [74, 75]. The only RCT of corticosteroids in nephrotic IgAN confirmed this approach, since there was remission of proteinuria only in patients with minimal glomerular change on light microscopy [76]. More recent RCTs of corticosteroids in IgAN have excluded those with nephrotic-range proteinuria, so there is little evidence to inform treatment choices for nephrotic IgAN with significant histologic glomerular injury.

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Evidence in Children

A number of reports have also described the association of mesangial IgA deposition in association with steroid-responsive nephrotic syndrome in children [77–79]. In at least two of the patients described in the SPNSG report, there was a temporal dissociation between the onset and course of nephrotic syndrome and the later development of clinical features of IgAN [77].

Patients with Slowly Progressive Renal Impairment

Recommendations for Adults

Tight BP control to a target of <125/75 mmHg and evaluation of individual cardiovascular risk are essential in this group of patients (strong recommendation, high level of evidence). In patients with persistent proteinuria (>1 g/24 h) despite tight BP control (<125/75 mmHg) and maximal RAS blockade (independent of BP), a 6-month treatment course of corticosteroids may reduce proteinuria and stabilize kidney function (weak recommendation, low level of evidence). Available evidence does not support a role for mycophenolate mofetil (MMF) in Caucasian patients (weak recommendation, very low level of evidence), although evidence from a single Chinese study suggests MMF may be useful as a steroid sparing agent in selected cases of IgAN in Chinese patients. We cannot recommend the use of cyclophosphamide (strong recommendation, low level of evidence), fish oil (weak recommendation, very low level of evidence), and other agents at the present time (Table 17.4).

Recommendations for Children

Based upon the limited evidence currently available, we are unable to make a specific recommendation regarding

Table 17.4 Treatment for IgA nephropathy.

Treatment	Recommendation	Certainty of evidence	Strength of recommendation
Angiotensin converting enzyme inhibitors or angiotensin II receptor blockers	We suggest angiotensin converting enzyme inhibitors or angiotensin II receptor blockers be used to lower blood pressure to <125/75 to 130/80 and/or maximize reduction of proteinuria for patients with IgAN	*High* (decrease in eGFR and proteinuria)	Strong
Tonsillectomy	We do not suggest tonsillectomy to be considered routinely in patients with IgAN	*Low* (decrease in eGFR and proteinuria)	Weak
Corticosteroids	We suggest in patients with progressive decline in eGFR and/or persistent proteinuria (>1 g/24 h) despite tight BP control (<125/75 mmHg) and maximal RAS blockade, a 6-month treatment course of corticosteroids may reduce proteinuria and stabilize kidney function	*Low* (decrease in eGFR and proteinuria)	Weak
Cyclophosphamide and azathioprine	We suggest crescentic IgAN associated with active glomerular inflammation and deteriorating renal function in the absence of significant chronic damage should be treated with induction therapy comprising cyclophosphamide and corticosteroids followed by maintenance therapy of azathioprine and corticosteroids at doses similar to those used for the treatment of ANCA-positive small vessel vasculitis	*Low* (decrease in eGFR and proteinuria)	Weak
Mycophenolate mofetil	We do not suggest mycophenolate mofetil be used in patients with IgAN	*Very low* (decrease in eGFR and proteinuria)	Weak
Fish oil	We do not suggest that fish oil be used in patients with IgAN	*Very low* (decrease in eGFR and proteinuria)	Weak

eGFR, estimated glomerular filtration rate; IgAN, IgA nephropathy; BP, blood pressure; RAS, renin angiotensin system; ANCA, anti-neutrophil cytoplasmic antibody.
GRADE assessment of the certainty of the evidence [5]: High: this research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different* is low. Moderate: this research provides a good indication of the likely effect. The likelihood that the effect will be substantially different* is moderate. Low: this research provides some indication of the likely effect. However, the likelihood that it will be substantially different* is high. Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different* is very high. **Substantially different = a large enough difference that it might affect decision-making*.

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the use of fish oil supplements for treatment of IgAN in the pediatric patient, although preliminary data from the North American IgA Nephropathy Trials indicate that such therapy may be efficacious in reducing proteinuria in such patients [77]. We recommend that a trial of alternate-day prednisone be considered in pediatric patients who have deterioration of GFR or persistent proteinuria (weak recommendation, very low level of evidence). If prednisone alone is unhelpful, we recommend therapy combining corticosteroids with azathioprine (weak recommendation, very low level of evidence)

Evidence in Adults and Children

Patients at risk of progressive renal dysfunction are typically those with hypertension, proteinuria of >1 g/24 h, reduced GFR at the time of diagnosis, and high Oxford scores in the diagnostic renal biopsy (M1, E1, S1, C1/2, and T1/2). Specific treatment strategies in this group of patients remain contentious. Progression is usually slow and therefore large studies with prolonged follow-up are necessary to evaluate new treatment strategies in these patients. Reported RCTs have tested interventions intended to slow immune and inflammatory events implicated in progressive IgAN, including corticosteroids, cyclophosphamide, and MMF. Because of the long duration required to identify with confidence the benefit of interventions, it is inevitable that recruitment into a number of these studies goes back 10 years or more, to a time when the generic approach to progressive glomerular disease was less well defined, so that BP targets and the use of RAS blockade are variable in these studies.

Immunosuppressive Treatments in Adults

The value of immunosuppressive treatment, in addition to best supportive therapy, in IgAN remains uncertain. The Supportive Versus Immunosuppressive Therapy for Progressive IgA Nephropathy (STOP-IgAN) trial was a multicenter, open-label, RCT in which immunosuppressive therapy added to comprehensive supportive therapy was compared with comprehensive supportive therapy alone in IgAN [80]. During a 6-month run-in period, patients received optimal comprehensive supportive care. Patients with persistent urinary protein excretion of >0.75 g/day were assigned randomly to continue comprehensive supportive care alone or comprehensive supportive care plus immunosuppressive therapy for 3 years. In the immunosuppression group, patients with an eGFR of 60 ml/min or greater received corticosteroid monotherapy for 6 months, and patients with an eGFR of 30–59 ml/min received cyclophosphamide for 3 months followed by azathioprine plus oral prednisolone. At 3 years there was no difference in either the number of patients who had a decrease in eGFR of at least 15 ml/min or the annual rate of decline in eGFR between the two groups. The glucocorticoid monotherapy arm produced a transient reduction in proteinuria in patients with relatively well-preserved GFR, but the reduction in proteinuria did not translate into protection against GFR decline. Adverse events (severe infections, impaired glucose tolerance, and weight gain of >5 kg in the first year of treatment) were more common in the immunosuppression group and one patient in the immunosuppression group died of sepsis.

Corticosteroids in Adults

The review of immunosuppressive treatments for IgAN by the Cochrane Renal Group identified six RCTs of sufficient quality to be included in their meta-analysis of corticosteroid treatment in IgAN (Table 17.5) [86]. This analysis suggests that corticosteroid therapy may be effective in reducing proteinuria (six trials, 263 patients) and reducing risk of ESRD (six trials, 341 patients), although the meta-analysis was unable to evaluate the influence of RAS blockade or achieved BP in the analysis. Follow-up in a large Italian study of corticosteroid treatment has now reached 10 years and the investigators report impressive benefit of treatment in reducing proteinuria and preventing ESRD [87]. However, the high-dose corticosteroid regimen, with pulse methylprednisone (1 g daily for 3 days at induction and beginning of months 2 and 4) and alternate-day oral prednisone (0.5 mg/kg) for 6 months, is regarded by many physicians as likely to carry considerable toxicity, even though none was reported by the investigators. Notably, RAS blockade was only used in a minority of patients in this study, although equally distributed among the participants, and achieved BP was not in line with current recommendations. Another RCT of corticosteroids (20 mg/day induction and 5 mg/day maintenance) from Japan in which BP control was tight even though RAS blockade was not used showed only a modest reduction in proteinuria with no protection of GFR [83]. It is unclear whether this lack of renoprotection was due to the lower dose of corticosteroid or a genuine lack of effect in patients managed to current BP targets. In a meta-analysis, consisting of nine studies and 536 patients, Lv et al. found that steroids therapy was associated with lower risk of developing kidney failure and reduction in proteinuria, but a 55% higher risk for adverse events [88].

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Table 17.5 RCTs included in the Cochrane Renal Group meta-analysis evaluating the benefit of corticosteroids in IgAN[a].

Author [reference]	*n*	Treatment	Follow-up (months)	Results
Julian [81]	35	Pred, 60 mg/alt day (3/12) Controls: no treatment	6–24	Stabilized GFR, ↓ proteinuria
Kobayashi [82]	46	Pred, 40 mg/day (tapering over 7/12) Controls: no treatment	120	Stabilized GFR, ↓ proteinuria
Katafuchi [83]	90	Pred, 20 mg/day (tapering to 5 mg/day over 24/12) Controls: dipyridamole 150–300 mg/day	60	No effect on GFR decline, ↓ proteinuria
Lai [76]	34	Pred, 40–60 mg/day (halved at 2/12 for further 2/12) Controls: no treatment	38	Stabilized GFR, ↓ proteinuria
Pozzi [84]	86	MP, 1 g IV 3 times then 0.5 mg/kg/day for 6/12 Controls: no treatment	60	Stabilized GFR, ↓ proteinuria
Shoji [85]	21	Pred, 0.8 mg/kg/day (tapering to 10 mg alt day for 12/12) Controls: dipyridamole 300 mg/day (12/12)	13	Stabilized GFR, ↓ proteinuria

GFR, glomerular filtration rate; MP, methylprednisone; Pred, prednisone.
[a] Overall quality low: inconsistent effects, variable quality of RCT design and reporting, small studies, surrogate outcomes.

The Therapeutic Evaluation of Steroids in IgA Nephropathy Global (TESTING) study was a multicenter, double-blind placebo-controlled RCT in which the efficacy and safety of methylprednisolone (0.6–0.8 mg/kg/day, maximum 48 mg/day) was assessed in patients with IgAN [89]. At entry proteinuria was >1 g/24 h and eGFR of 20–120 ml/min after at least 3 months of BP control with RAS blockade. The study almost exclusively recruited form China and was terminated prematurely due to an excess of serious adverse events, mostly serious infections, including two deaths in the methylprednisolone group. While there did appear to be a potential renal benefit of oral methylprednisolone with a decrease in the primary composite outcome of ESRD, death resulting from kidney failure, or a 40% decrease in eGFR, a definitive conclusion could not be made because of early termination of the study. A low-dose TESTING study (ClinicalTrials.gov identifier NCT01560052) is now recruiting using half-dose methylprednisolone with co-trimoxazole prophylaxis and is expected to report in 2021/2.

Corticosteroids in Children

The short-term effects of prednisone on proteinuria and hematuria were examined by Welch et al. in a group of children with IgAN. Twenty patients were randomized to either placebo or prednisone (2 mg/kg/day, maximum 80 mg) for 2 weeks, followed by the same dose on alternate days for 10 weeks [90]. After a 12-week washout period, the treatments were reversed in each subject. No difference in the severity of hematuria was reported after treatment with prednisone compared to placebo. However, most of the subjects had only mild histologic changes, and the subjects in this study would not be expected to have progressive disease.

Waldo et al. compared the outcomes of 13 children with IgAN in Alabama followed for 4–10 years after they received alternate-day prednisone for 2 years with 15 children in Tennessee who received no steroid therapy [41]. All of the patients had either proteinuria of >1 g/m^2/day or renal biopsies showing more than a minimal degree of interstitial fibrosis, tubular atrophy, or glomerular sclerosis. None of the 13 treated patients progressed to ESRD, compared to five of 15 of the untreated patients ($P = 0.04$). At last follow-up, 12 of 13 treated patients had no hematuria and normal protein excretion ($P < 0.001$ compared with nontreated historic control patients).

Cyclophosphamide with/without Azathioprine in Adults

The use of cyclophosphamide in patients at very high risk of progression (ESRD predicted in all cases within 5 years) is supported by a single study. Patients received cyclophosphamide (1.5 mg/kg/day for 3 months) followed by azathioprine (1.5 mg/kg/day) in conjunction with high-dose prednisone (40 mg/day induction, 10 mg/day maintenance) and were followed for at least 2 years [91]. Notably, BP control and use of RAS blockade in this trial fell outside current recommendations. Previous RCTs of cyclophosphamide in less severe, slowly progressive IgAN have shown no consistent benefit [92], and this is supported by the STOP-IgAN trial and a Cochrane Renal Group meta-analysis, which failed to show any significant renal survival benefit from those RCTs incorporating cyclophosphamide,

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cyclosporine, or other cytotoxic agents, although there was a significant reduction in daily proteinuria [80, 93]. These studies were, however, insufficiently powered to exclude any effect on progression with certainty.

Cyclophosphamide with/without Azathioprine in Children

The efficacy of a 1-year combined course of prednisone and azathioprine was evaluated in 10 children with IgAN by Andreoli and Bergstein [94]. Prednisone at 60 mg/m^2 (maximum 60 mg) daily for 8 weeks was followed by the same dose every other day for 10 months. Azathioprine (2–3 mg/kg/day) was given for 12 months. Proteinuria decreased significantly after treatment and serial renal biopsies showed that the activity score improved, but the chronicity score was unchanged. The level of microscopic hematuria also improved.

In 1994, Murakami et al. evaluated the efficacy of a 6-month course of prednisolone at 10–15 mg on alternate days, cyclophosphamide at 1 mg/kg/day, and dipyridamole at 5 mg/kg/day in 17 patients who had proteinuria of >1 g/m^2/day plus histologic risk factors for progressive disease compared to 21 patients with similar features who received the same regimen plus warfarin for 3 months [95]. The dipyridamole therapy was subsequently continued in all patients until the patient had ≤1 g/m^2/day proteinuria. Both groups of patients showed significant improvement in proteinuria but the chronic histology indices on post therapy biopsies (14 patients) showed persistent signs of chronic disease, as with Andreoli and Bergstein [94]. Addionally, follow-up studies showed rebound deterioration of proteinuria after 5–6 years.

In 1999, Yoshikawa et al. reported an RCT evaluating 2 years of therapy in two groups of children: group 1 prednisone, azathioprine, heparin, warfarin, and dipyridamole; group 2 heparin, warfarin, and dipyridamole [40]. The prednisone dose was 2 mg/kg/day (maximum 80 mg) for 4 weeks, reduced over 8 weeks, then maintained at 1 mg/kg every other day for 21 months. The azathioprine dose was 2 mg/kg/day. Although there was no significant change in GFR in either group, group 1 patients had a significant reduction of proteinuria but those in group 2 did not. There was also a significant decrease in glomerular IgA staining in follow-up biopsies in group 1 patients but not in group 2. These follow-up biopsies showed progression of glomerular sclerosis in control patients but not in those receiving prednisone and azathioprine. More recently, in 2006, Yoshikawa et al. described the results of a second RCT that compared the effects of combination therapy using prednisone, azathioprine, warfarin, and dipyridamole in 40 children versus prednisone alone in 40 children over 24 months [96]. Both treatment regimens were associated with remarkable improvement in proteinuria. The percentage of glomeruli showing sclerotic changes was unchanged from baseline in the patients receiving combination therapy but significantly higher in those receiving only prednisone. However, the use of ACEi/ARB was prohibited in this trial, hence it is not clear whether such aggressive immunosuppressive therapy would be the first choice of therapy in clinical practice.

MMF and Mizoribine in Adults and Children

MMF has been used in six major trials for IgAN (Table 17.6). Two studies reported no benefit from MMF (2 g/day) in Caucasian patients either at risk of progression (hypertensive and/or proteinuria of >1 g/24 h and/or reduced GFR within 5 years of diagnosis) [97] or with more advanced

Table 17.6 Evidence for the use of MMF in IgAN[a].

Author [reference]	Design	*n*	MMF treatment	Follow-up (months)	Results
Maes [97]	RCT	34	2 g/day for 36/12	36	No effect on GFR decline, no effect on proteinuria
Chen [98]	RCT	93	1–1.5 g/day for 6/12 1 g/day for 6/12 0.75 g/day for 6/12	18	No effect on GFR decline, ↓ proteinuria
Tang [99]	RCT	40	2 g/day for 6/12	18	No effect on GFR decline, ↓ proteinuria
Frisch [100]	RCT	32	2 g/day for 12/12	24	No effect on GFR decline, no effect on proteinuria
Hogg [101]	RCT	44	25-36 mg/kg/day for 12/12	6 (early termination)	No effect on proteinuria
Hou [102]	RCT	176	1.5 g/day	12	No effect on proteinuria

GFR, glomerular filtration rate; RCT, randomized controlled trial.
[a] Overall quality low: inconsistent effects, variable quality of RCT design and reporting, small studies, surrogate outcomes.

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disease (mean serum creatinine at entry, 2.6 mg/dl) [100]. Both of these studies achieved rigorous BP control with use of an ACEi. In two separate studies in Chinese patients with less advanced renal impairment, MMF (1–2 g/day) did reduce proteinuria over an 18-month follow-up period, but neither study demonstrated a change in rate of renal decline [98, 99]. Again, both studies achieved tight BP control with ACE inhibition. A more recent study examined the use of MMF versus placebo in Caucasian adults and children in addition to lisinopril/losartan plus highly purified omega-3 fatty acid. The trial was terminated early because of a lack of benefit [101]. In a Chinese study, MMF and low-dose prednisolone (0.4–0.6 mg/kg per day) was compared with full dose prednisolone (0.8–1 mg/kg per day). Both regimens had equal efficacy in terms of remission rates at 6 and 12 months [102]. However, the MMF and steroid group suffered significantly fewer adverse events, suggesting MMF could be used as a steroid sparing agent in Chinese patients with IgAN.

A retrospective study in Japan showed that mizoribine, which blocks purine synthesis in a manner similar to MMF, resulted in a significant reduction in proteinuria when given to 20 pediatric patients in combination with prednisone, warfarin, and dipyridamole [103]. This was significantly better than the reduction in proteinuria seen in 21 historic control patients who were given only prednisone, warfarin, and dipyridamole, or in 20 historic control patients who also received IV pulses of methylprednisone. Follow-up renal biopsies in the mizoribine-treated patients showed no progression of chronic lesions, whereas the other two sets of patients had a significant increase in the chronicity index. A recent pilot study using mizoribine, again in combination with prednisone, warfarin, and dipyridamole, confirmed the efficacy and safety of this regimen in treating children with IgAN [104].

Fish Oil in Adults

A number of studies have evaluated the role of fish oils (eicos-apentanoic acid and docosahexanoic acid) in IgAN (Table 17.7). An RCT of 106 patients with proteinuria of >1 g/24 h and impaired renal function at enrollment (60% also hypertensive) found those treated with fish oil had a slower rate of decline in GFR at both 2 and 5 years [107, 108]. This effect appeared independent of the dose used [109]. These results have not been replicated in other RCTs studying similar patient cohorts [42, 105, 106]. A meta-analysis (three trials, 175 patients [105–107]) failed to detect a benefit of fish oils on renal outcome in IgAN [110]. Furthermore, a recent RCT showed no benefit following 2 years of treatment with fish oil compared to placebo [42], although a subsequent post hoc analysis of the data in the study revealed a dose-dependent decrease in proteinuria in the fish oil group [108]. In a Cochrane meta-analysis, consisting of four studies with 256 participants, there was no overall benefit of fish oil, as compared to placebo or no treatment, on renal outcomes, including change in serum creatinine, creatinine clearance, and decrease in proteinuria [111].

Rituximab

The role of rituximab in the treatment of patients with IgA nephropathy was evaluated in an open-label randomized study of 34 patients. Patients were randomly assigned to receive two doses of rituximab 1 g administered 2 weeks apart and an identical course 6 months later, or no rituximab. Despite successful depletion of CD19+ B cells, there were no differences in the change in proteinuria or change in renal function from baseline between the two groups [112].

Table 17.7 Evidence for the use of fish oil in IgAN[a].

Author [reference]	Design	*n*	EPA + DHA daily doses (g)	Follow-up (months)	Results
Bennett [105]	RCT	37	1.8 + 1.2	24	No effect on GFR decline
Pettersson [106]	RCT	32	3.3 + 1.8	6	↓ GFR, no effect on proteinuria
Donadio [107, 108]	RCT	106	1.8 + 1.2	24 and 60	Slower ↓ GFR
Donadio [109]	RCT	73	3.8 + 2.9 1.9 + 1.5	24	No difference between high- and low-dose EPA–DHA
Hogg [42]	RCT	96	1.88 + 1.48	24	No effect on GFR decline, ↓ proteinuria

DHA, docosahexanoic acid; EPA, eicosapentanoic acid; GFR, glomerular filtration rate; RCT, randomized controlled trial.
[a] Overall quality low: inconsistent effects, variable quality of RCT design and reporting, small studies, surrogate outcomes.

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Other Therapies

Warfarin, urokinase, antiplatelet agents, phenytoin, sodium cromoglycate, dietary gluten restriction, and a low-antigen content diet have all been assessed for the treatment of IgAN and have not been shown to affect renal outcomes [92].

The use of newer immunosuppressive agents, such as the targeted release formulation of budesonide (ClinicalTrials.gov identifier NCT03643965), fostamatinib (ClinicalTrials.gov identifier NCT02112838), sparsentan, OMS721 (ClinicalTrials.gov identifier NCT03608033), LNP023 (ClinicalTrials.gov identifier NCT03373461), blisibimod (ClinicalTrials.gov identifier NCT02062684), and atacicept (ClinicalTrials.gov identifier NCT02808429), while of potential interest for this group of patients, should be considered experimental therapies at this point.

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18

Membranoproliferative Glomerulonephritis

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Introduction

The term membranoproliferative glomerulonephritis (MPGN) refers to a morphological pattern of injury common to a heterogeneous group of diseases; it is also known as "mesangiocapillary glomerulonephritis" or "lobular glomerulonephritis." Light microscopy examination shows glomerular injury which consists of increased mesangial matrix accompanied by an increase in the cellularity of the mesangium and capillary-wall remodeling. These changes result in lobular accentuation of the glomerular tufts.

Based on the results provided by electron microscopy, MPGN has been conventionally categorized as primary (idiopathic) type I, type II, or type III. The most common form of MPGN is MPGN I, which is characterized by subendothelial deposits (often presumed to be immune complexes); MPGN type III has both subendothelial and subepithelial deposits. MPGN type II has dense deposits in the glomerular basement membrane ("dense deposit disease") [1].

A more recent classification is based on the composition of the deposits, as highlighted by immunofluorescence staining [2–4]. This classification results from an enhanced understanding of the role of complement in the pathogenesis of MPGN, and treatments targeting specific diseases are under way. This chapter reviews the most important advances regarding pathogenesis, prognosis, and current therapeutic options for MPGN and some additional MPGN-associated conditions.

MPGN: Histology

The morphological pattern of MPGN includes a marked and diffuse thickening of the glomerular capillary walls. The thickening can be more prominent in some glomeruli and in some capillary loops than in others. Periodic acid Schiff and silver methenamine stains show that the thickened glomerular capillary walls sometimes have two basement membranes with a clear nonargyrophylic region between them. The double contour is termed duplication of the glomerular basement membrane; interposition of mesangial cells or trapping of circulating cells between various layers of basement membrane commonly occurs. In some capillaries, the duplication of the glomerular basement membrane results in multiple laminations. The thickening of the capillary walls, the mesangial expansion (increase in matrix and cellularity in mesangium), and the occurrence of subendothelial deposits lower the glomerular capillary lumen. These abnormalities are most often diffuse and generalized, and lead to a simplification of the architecture of the glomeruli and an accentuation of the lobulation of the glomerular capillaries. Extracapillary crescent formation can complicate the histological picture in approximately 10% of patients. These are frequently small and focal crescents. Morphological changes in the tubules and interstitium typically reflect the changes noted in the glomeruli. Arterial and arterioles are affected in cases with renal failure and long-standing hypertension. The strong association between MPGN and hypocomplementemia has been highlighted by West and coworkers in

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1965 and led to the adoption of the term "hypocomplementemic persistent glomerulonephritis" for this subset of glomerular disorders [5].

MPGN: Novel Classification and Pathophysiology

According to the novel classification, three types of MPGN have been suggested: (i) immune-complex-mediated MPGN, (ii) complement-mediated MPGN, and (iii) nonimmune-complex mediated/noncomplement mediated MPGN [2–4] (Figure 18.1).

Patients with immune-complex-mediated MPGN (IC-MPGN) typically show at kidney biopsy immunoglobulin and complement on immunofluorescence staining. Immune-complex mediated MPGN is further subdivided depending on the Ig structure (i.e. monoclonal IgG heavy chain or polyclonal IgG, as in lupus nephritis). When an autoimmune disease such as lupus is the underlying disorder, MPGN is characterized by a "full house" pattern of immunoglobulin deposition including IgG, IgM, IgA, C1q, C3, and kappa/lambda chains [6]. Immune-complex-mediated MPGN includes most of those cases formerly considered MPGN type I and some cases of MPGN type III (Burkholder type). The absence of marked immunoglobulin staining on immunofluorescence microscopy distinguishes MPGN due to alternative-pathway dysfunction from immune-complex-mediated MPGN. Indeed, complement-mediated MPGN is typically immunoglobulin-negative but complement-positive on immunofluorescence studies; it is associated with dysregulation of the alternative pathway of complement. On the basis of electron microscopy, complement-mediated MPGN or $C3_3$ glomerulopathy (C3G) may be classified into dense-deposit disease (DDD) and C3 glomerular disease (C3GN). Cases of the former MPGN type II (DDD) and some cases of MPGN type III (Strife and Anders type) are included in the subset of complement-mediated MPGN.

An additional category is nonimmune-complex mediated/noncomplement-mediated MPGN. Glomerular lesions consistent with MPGN are very infrequent and confined to a few patients of chronic thrombotic microangiopathies, de novo chronic transplant nephropathy, radiation nephritis, or drug-associated thrombotic angiopathy. In these cases, immunofluorescence is typically negative for immunoglobulins and complement, and electron-dense deposits are not detected by electron microscopy (Figure 18.1).

Immune-complex-mediated MPGN

Immune-complex-mediated MPGN is typically a consequence of the deposition of immune complexes in the glomeruli owing to persistent antigenemia, with antigen-antibody immune complexes forming as a result of chronic infections, elevated levels of circulating immune complexes due to autoimmune diseases, or paraproteinemias due to monoclonal gammopathies. Then, the immune complexes activate the classical complement pathway and this is clinically reflected in a normal or mildly decreased serum C_3 concentration and a low C_4 level. The most frequent underlying disorders linked with immune-complex MPGN are infections and these include hepatitis B [7] or C virus (with or without cryoglobulinemia) [8, 9], bacterial, or protozoal agents (Table 18.1). In addition, autoimmune disorders involved in the pathogenesis of MPGN are

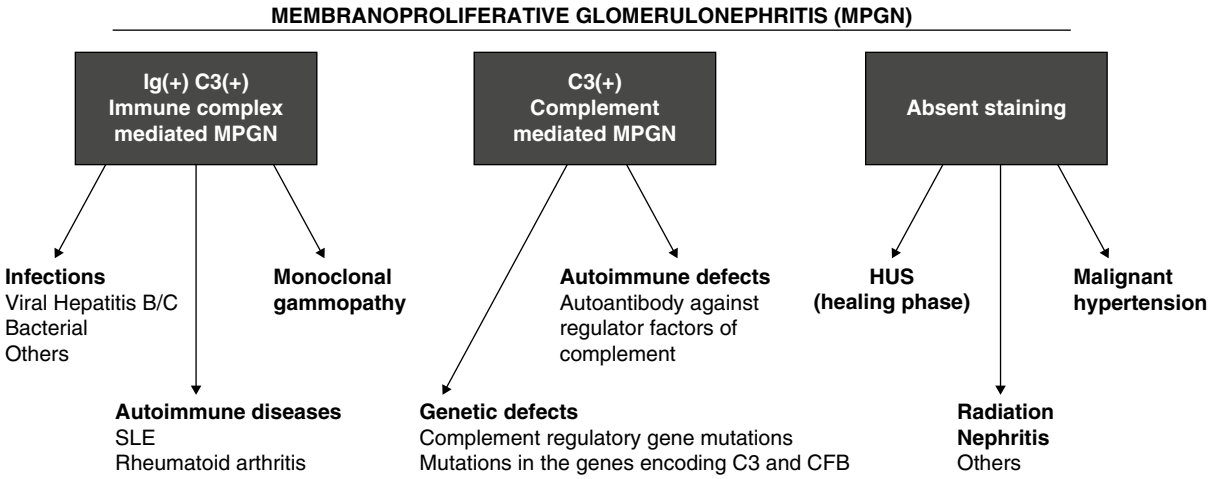

Figure 18.1 Classification of membranoproliferative glomerulonephritis and etiologies.

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Table 18.1 Infectious agents associated with MPGN.

Bacterial infections
Escherichia coli
Leptospirosis
Pseurodomonas aeruginosa
Salmonella typhi
Staphylococcus (aureus, albus)
Streptococcus (group A, *viridans)*
Viral infections
Hepatitis C
Hepatitis B
Hepatitis E
Coxsackie virus
Parvovirus
Parasitic infestation
Schistosoma mansoni or haematobium
Toxoplasmosis
Plasmodium falciparum or malariae
Other infectious organisms
Candida albicans
Coxiella

rheumathoid arthritis and systemic lupus erythematosus. Additional causes of MPGN are monoclonal gammopathies (mostly of uncertain significance) and malignancies (renal cell carcinoma, non-Hodgkin lymphoma) [10–14].

The diagnosis of idiopathic MPGN is made after all of the secondary causes are excluded; idiopathic MPGN is considered now a rare entity and the majority of cases of immune-complex-mediated MPGN are secondary to the etiologies reported above.

HCV-associated Immune-complex-mediated MPGN

Hepatitis C virus (HCV) may instigate mixed cryoglobulinemia and the most significant accompanying kidney lesion is type I MPGN, usually occurring in the context of type II mixed cryoglobulinemia. Patients with type II MC show monoclonal IgM *k* (or IgG or IgA) having rheumatoid factor (RF) activity and polyclonal Ig (mainly IgG). After the identification of HCV, it has been recognized as the cause of 80–90% of mixed cryoglobulinemia. In the absence of an identified etiologic factor (<5% of all mixed cryoglobulinemia), cryoglobulinemic vasculitis is defined as essential or idiopathic. The most common symptoms of MC syndrome are weakness, arthralgias, and purpura, also called Meltzer's triad. The dermatologic manifestations of MC can vary from simple cutaneous palpable purpura to complex confluent lesions (Figure 18.2), including ulceration of the skin.

Although extrarenal signs of mixed cryoglobulinemic vasculitis usually precede the kidney manifestations, often by years, in 29% of cases kidney and extrarenal involvement are concurrent. Kidney involvement in mixed cryoglobulinemia occurs in 8–58% of patients, and in a minority of cases kidney disease can be the first manifestation of MC. More than half the patients have proteinuria and/or hematuria only. A "nephritic" syndrome is diagnosed in around 20% of cases. Hypertension is common and may be severe, affecting >50% of patients at the time of diagnosis. In 10% of patients, acute oliguric kidney failure is the first indicator of kidney disease. Often both nephrotic proteinuria and active urinary sediment with elevated serum creatinine are present simultaneously. Of particular importance is the development of kidney disease because patients with cryoglobulinemic nephritis have a poor prognosis, mainly because of a high incidence of infections, end-stage liver and cardiovascular diseases.

Roccatello et al. [8] evaluated 146 patients with cryoglobulinemic nephritis, of whom 87% ($n = 127$) were HCV positive, and noted type II cryoglobulins (IgG/IgM-*k*) in

Figure 18.2 Confluent purpura (right inferior limb: distal portion thigh and proximal leg) in HCV-related MPGN.

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74.4% of cases; the rest had type III cryoglobulins. The most common histologic pattern was diffuse MPGN (83%). Survival at 10 years was only 30%, with cardiovascular disease the cause of death in >60% of patients. Additional causes of death included infections (10%), liver failure (19%), and neoplasia (3%). Another survey by Tarantino et al. ($n = 105$ patients) gave different results, with deaths caused by infections (21%) and liver failure (19%) nearly as common as those caused by cardiovascular diseases (29%) [15]. Differences in antibiotics or immunosuppressive agents could explain these differences.

Complement-mediated MPGN or C3 Glomerulopathy

C3G encompasses glomerular diseases associated with persistent activation of the alternative complement pathway [3, 16, 17]. Kidney biopsy findings are characterized by the occurrence of glomerular deposits, mostly composed of C3, and no staining for immunoglobulins or for components of the classical pathway of complement activation.

The complement system includes three pathways, the classical, lectin and alternative pathways, and patients with C3G have abnormal control of the alternative pathway of complement (Figure 18.3). The most important protein in the circulation that controls the alternative pathway is complement factor H (CFH); mice engineered to lack CFH have undetectable circulating C3 because their C3 is persistently consumed by an uncontrolled complement activation (alternative pathway) [18].

It has been recently discovered that mutations in genes encoding proteins of the alternative complement pathway (AP) occur in more than 50% of patients with atypical hemolytic uremic syndrome (aHUS) and in approximately 20% of patients with MPGN [16]. Complement gene abnormalities associated with aHUS most commonly result in complement dysregulation restricted to the cell surface, whereas complement activation in the fluid phase is more common in most genetic cases of MPGN [16]. These acquisitions have highlighted the role of genetic variations in the complement system in determining predisposition to glomerular injury. Hyperactivation of the alternative pathway of the complement system as observed in deposit dense disease (DDD) or C3 glomerulonephritis (GN) has been often associated with multiple mutations in inhibitors of the alternative pathway, including factor H, factor I, CD46 (membrane cofactor protein [MCP]), and the factor–H-related protein family (CFHR, 2, 3, 4, and 5). CFHRs are a group of closely related proteins controlling the activity of factor H; it appears now that CFHRs are able to antagonize the CFH action. Many patients with C3G show failure of CFH to control the activation of the alternative pathway in the circulation, thus they have low levels of serum C3 due to exaggerated consumption.

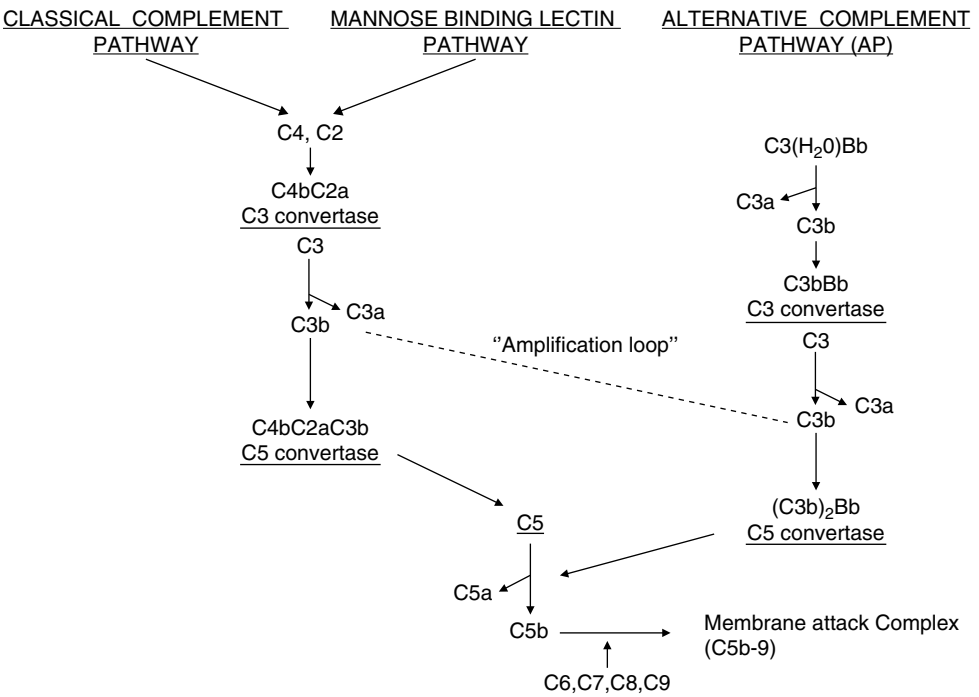

Figure 18.3 Complement cascade (the three complement pathways).

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An increased activation of the AP has been also linked with the occurrence of auto-antibodies against various components of the complement system: anti-CFH, anti--CFB (anti-complement factor B), anti-C4, or anti-C3b. These antibodies activate the alternative pathway either by stabilizing C3 convertase (such as C3 nephritic factor, C3NF) or its components against CFH. C3NFs are a group of autoantibodies that bind to the AP C3 convertase (C3bBb), increasing both convertase activity and the duration of the active forms, making it more stable (from minutes to hours) [16, 17]. These autoantibodies can be detected by using C3 convertase stabilizing activities, semiquantitative hemolytic assays, by measuring autoantibody levels. There are various types of C3NFs, including both IgM and IgG, which can be classified by either being heat sensitive and properdin dependent or heat stable and properdin independent. The clinical significance of C3Nefs remains unclear. More than 80% of patients with dense-deposit disease (DDD) and 40–50% with C3 glomerulonephritis (C3GN) have C3NFs; however, their association with disease outcome gave conflicting results. Alternatively, autoantibody can block the activity of pathway inhibitors (such as antifactor H autoantibody) [17]. A familial type of C3 glomerulopathy is CFHR5 nephropathy, where the mutation is a duplication of the first two exons of the CFHR5 gene [19].

The most recent view is that the dysregulation of the AP may be familiar or triggered by external factors. A genetic or acquired defect in complement regulatory proteins if severe enough may lead to the disease process. On the other hand, a genetic mutation with incomplete penetrance might need an environmental trigger to start with the disease. The most common environmental triggers are infections, surgery, autoimmune disease flares, vaccinations, pregnancy, and postpartum state. Thus, genetic mutations affecting the regulatory proteins of the AP (CFH, I, membrane co-factor protein, CFH related proteins, among others) and triggers result in the clinical manifestations of DDD and C3GN.

C3G, Dense Deposit Disease, and C3GN

DDD is characterized by osmiophilic deposits that replace the glomerular basement membrane and also occur in the mesangium; C3G without the characteristic appearances of DDD is called C3 glomerulonephritis (C3GN). C3GN has frequently mesangial, subendothelial, and sometimes subepithelial and intramembranous deposits. It has been suggested that DDD and C3GN are part of a continuum. Histological features intermediate between DDD and C3GN have been reported: some capillary loops show intramembranous dense deposits and others have subendothelial and subepithelial deposits on electron microscopy. Patients with DDD have dark, ribbon-like osmiophilic deposits within the glomerular basement membrane. DDD is typically a disease of children and C3 is frequently depressed (79% in DDD vs. 48% in C3 GN). DDD is frequently associated with extrarenal abnormalities such as partial lypodystrophy or drusen, which is similar to age-related macular degeneration. Ocular drusen are yellow deposits under the retina and are made of lipids and fatty proteins. Drusen likely do not cause age-related macular degeneration; however, patients with ocular drusen are at risk of developing age-related macular degeneration. A few patients with DDD have partial lipodystrophy (APL) which is characterized by symmetric loss of adipose tissue from upper portions of the trunk, face, and arms.

The most common pathological lesion in C3GN is MPGN, but other patients of glomerular damage have been reported, including mesangio-proliferative GN, diffuse endocapillary GN, focal segmental glomerulosclerosis, and crescentic GN [20].

There is a paucity of data regarding the natural history and outcome of C3 glomerulopathy. It is an infrequent renal disorder and its classification has been recently updated. The outcome of C3 glomerulopathy has been retrospectively addressed in a large ($n = 111$) cohort of patients, 87 with C3GN and 24 with DDD [21]. Complement-associated gene variants and auto-antibodies were detected in 24% and 35% of patients, respectively. Over an average observation period of 72 months, remission occurred in 38% of patients with C_3GN and 25% of patients with DDD. Progression to end-stage renal disease (ESRD) was frequent, and no differences between C3GN (39%) and DDD (42%) were found. Multivariate analysis showed that eGFR at diagnosis and tubular atrophy/interstitial fibrosis were the strongest predictors for progression to ESRD. Medjeral-Thomas and coworkers in a European cohort of 80 patients with C3 glomerulopathy (21 with DDD and 59 with C3GN) observed that patients with DDD were younger, more likely to have low serum C3 levels, and more likely to have crescentic GN than patients with C3GN [22]. Median follow-up, censored for ESRD development, in the remaining cohort ($n = 70$) was 28 months (interquartile range 7–84) without any significant difference in median follow-up duration between subgroups. At last follow-up, 20 patients progressed to ESRD (47% of patients with DDD and 23% of patients with C3GN). Cumulative renal survival did not, however, differ between groups by Kaplan–Meier survival analysis. Age > 16 years ($P < 0.04$), DDD subtype ($P < 0.03$), and crescentic GN ($P < 0.01$) were independent predictors of ESRD within the

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entire cohort. DDD recurs very frequently after renal transplant; it has been calculated that approximately 45% of patients lose their allograft within 5 years after transplant due to the recurrence of the disease.

MPGN: Clinical Presentation and Natural History

The clinical manifestations of patients with MPGN are highly variable and similar to those reported in other types of glomerular diseases. Patients can show microscopic hematuria with or without mild proteinuria. Proteinuria in the nephrotic range or even full brown nephrotic syndrome with or without hypertension and low glomerular filtration rate (GFR) may occur. It may also present with macroscopic hematuria with or without a fast worsening of the renal function (particularly when crescents are present at histology). The discovery of hypocomplementemia (reduced levels of C3 and/or C4 or lowered C/H50) is a frequent feature which characterizes most MPGN forms in comparison with the other idiopathic glomerular diseases (minimal change disease, focal and segmental glomerulosclerosis, membranous nephropathy, and IgA nephropathy seldom, if ever, display hypocomplementemia).

Clinical factors which are associated with a progressive course leading to ESRD include persistence of nephrotic-range proteinuria (> 3 g/g of creatinine in a spot urine sample in an adult), the presence of arterial hypertension (AH) (blood pressure > 140/90 mmHg), and raised serum creatinine at baseline. In addition, marked hematuria (> 500 000 erythrocytes/ml of urine not centrifuged) is strongly associated with the presence of crescents, which confer a less favorable prognosis. Patients with MPGN who have intact kidneys at baseline and show persistent non-nephrotic proteinuria seldom progress to ESRD.

Kidney biopsy can provide some pathological features at the time of diagnosis which play a role in the outcome. An unfavorable course of MPGN is often associated with some kidney changes, including extensive crescent disease (>50% involvement of glomeruli), extensive glomerulosclerosis, tubulo-interstitial fibrosis, and tubular atrophy. Such findings often are strongly associated with an elevation of serum creatinine levels.

A contemporary analysis of the natural history of MPGN (unmodified by any specific therapy) and all of its varieties is extraordinarily difficult, and multiple reasons exist for this. The overall long-term renal survival (5 and 10 years after diagnosis) for untreated idiopathic MPGN can be reconstructed from reports in the literature. Some factors that limit the accuracy of these predictions include the following: (i) lead-time bias for patients discovered during screening; (ii) lack of stratification of patients into HCV-positive or negative cases; (iii) inclusion of patients treated with various regimens in observational studies of prognosis; (iv) lack of information concerning the degree of blood pressure control and the use of ace-inhibitors or angiotensin receptor blockers; (v) lack of detailed information on concomitant renal lesions affecting outcomes (e.g. crescentic involvement); and (vi) failure to stratify patients according to the presence and persistence of complement regulatory dysfunction, thrombotic microangiopathy, or monoclonal immunoglobulin deposition disease. For the last, the recent changes in the classification of MPGN with the identification of some additional MPGN-associated conditions are an additional impediment.

The analysis of the long-term renal survival (5- and 10-year after diagnosis) for idiopathic and untreated MPGN can be in part reconstructed from the medical literature. Placebo or untreated arms of the reported randomized controlled trials (RCTs) of specific therapies can give detailed information on this point. For example, in the open-label RCT of therapy for MPGN in children and adults reported by Cattran et al. in 1985, the control group ($n = 32$), who received no specific therapy, displayed a 2-year kidney survival of 85% in MPGN type I and 90% in MPGN type II. All of these patients had an initial creatinine clearance of <80 ml/min/1.73 m^2 and proteinuria of >2 g/day at baseline [23]. Of note, 8 of 32 control patients in this study obtained a spontaneous clinical remission. In the randomized, placebo-controlled trial of treatment of MPGN reported by Tarshish et al. the actuarial renal survival in the placebo group ($n = 40$) was only 12% at 130 months, and a progressive decline of renal function was noted in about 60% of the placebo group [24]. In the study by Tarshish and coworkers 52% had MPGN type I, 17% had MPGN type II, and 30% had MPGN type III or other types of MPGN. Donadio et al. carried out a randomized, double-blind placebo-controlled trial of therapy for MPGN type I. The average decline in GFR was 19.6 ml/min/year/1.73 m^2 in the placebo group [25]. A total of 9 of 19 patients in the placebo group developed ESRD after 33 months. The authors suggested that the poor outcome observed in the placebo group could be related to the long duration of disease prior to entry into the randomized trial.

Evidence coming from observational studies can also give some insight into the natural history of MPGN. In the study by Chan et al. 27 (59%) of 46 patients with MPGN (including 20% with hepatitis B surface infection) developed or died of ESRD within a follow-up period averaging 60 months, with no difference in outcome between treated ($n = 19$) and untreated ($n = 27$) patients [26]. Cansick et al. assessed the long-term outcome of 53 children with MPGN (58% type I, 26% type II, and 16% type III and others).

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The median follow-up was 3.3 years (range, 0–17 years). Twenty-nine of the 53 children were treated with corticosteroids with an uncontrolled design. Overall renal survival including the treated patients and patients without nephrotic syndrome was 92% at 5 years and 83% at 10 years. In the group of patients with nephrotic syndrome at discovery, the mean renal survival was 8.9 years compared to 13.6 years when nephrotic syndrome was absent [27].

In summary, it is difficult on the grounds of the current medical literature to establish a consistent pattern of long-term outcome for patients with MPGN who did not receive therapy. Overall renal survival of MPGN type I patients among treated and untreated patients averages about 60% at 10 years (range 50–80%), with adults having a less favorable outcome. Concomitant hepatitis B or C virus infection likely confers a worse prognosis.

Treatment

Idiopathic Immune-complex MPGN

As mentioned above, the term idiopathic MPGN in adults or children refers to cases of MPGN with an unknown cause. The Kidney Disease Improving Global Outcomes recommends making the diagnosis of idiopathic MPGN only after exclusion of any other identifiable cause [28]; the histological pattern of type I MPGN is most typical among patients with idiopathic MPGN. Also, the MPGN histological pattern is characterized by various clinical pictures. It appears that idiopathic MPGN is more frequent in less-developed countries, where infectious diseases are more common than among developed world. The management of secondary MPGN requires treatment of the primary disease, often in combination with immunosuppression.

The evidence regarding the treatment of idiopathic MPGN is not robust for numerous reasons. A few RCTs have been published, but all these studies were conducted a long time ago and do not conform to modern-day standards of excellence. Thus, many early reports of treatment of idiopathic MPGN probably included cases now categorized as secondary MPGN. Only six RCTs (involving fewer than 270 patients with MPGN) have been reported for MPGN to date (Table 18.2) [23–25, 29–33].

In short, the evidence currently coming from RCTs is weak (very low to low level), as already emphasized by others [34, 35]. For patients with *mild disease*, i.e. hematuria and low-level proteinuria (<500 mg/day), and normal or nearly normal kidney function, RAS inhibition with angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) should be made. In patients with *nephrotic syndrome* and intact kidney function, oral steroids (prednisone, 1 mg/kg/day of body weight) should be given for 12–16 weeks. Tapering of steroids should last for 6–8 months, but should be faster in patients with resistant disease. Cyclophoshamide should be considered according to the clinical response to steroids. In cases of *deterioration of kidney function*, oral steroids (according to the aforementioned dosage scheme) should be tried. If there is no response, oral cyclophosphamide (1–2 mg/kg body weight adjusted to eGFR) for 4–6 months or rituximab (RTX) (1 g × 2 on day 1 and 15) should be considered. In patients with *rapidly progressive glomerulonephritis*, with or without nephrotic syndrome, rescue therapy with intravenous steroids (methyprednisolone, 0.5–1 g/day for three consecutive days) has been suggested, followed by oral prednisone (1 mg/kg/day body weight) and cyclophosphamide.

Therapies based on ACEIs and ARBs are safe and have some efficacy in proteinuric patients. Some case series have been recently published regarding the treatment of idiopathic MPGN with alternative drugs, such as mycophenolate mofetil (MMF) (Table 18.3) [36–42], calcineurin inhibitors [43, 44], and monoclonal antibody (rituximab and imatinib) (Table 18.4) [45–50]. These drugs have been able to give some benefit to patients with idiopathic MPGN but we need RCTs on this point. Several questions remain unanswered, including dose and duration of therapy with these drugs, their role (first-line therapies or not), and their safety profile.

HBV- or HCV-associated MPGN

Patients with hepatitis B virus (HBV)-associated MPGN should receive antiviral therapy with nucleos(t)ide analogs (NUCs) and/or immunosuppressive therapy, according to the clinical presentation of the disease (Figure 18.4). Many patients with HCV-associated MPGN also have mixed cryoglobulinemia and they may also have overt chronic liver disease. All patients presenting with MPGN type I are now routinely tested for anti-HCV antibody (and HBsAg) and often are also examined for HCV RNA by reverse polymerase chain reaction. Thus, it should not be difficult to make a differential diagnosis between idiopathic forms of MPGN and those secondary to HCV or HBV.

The discovery of HCV and a better understanding of the mechanisms of disease has provided the opportunity to control HCV-induced glomerular disease (including MPGN) using targeted approaches: (i) antiviral therapy, supported by the notion that HCV infection stimulates the synthesis of immune complexes and the ensuing glomerular disease; (ii) B-cell depletion therapy targeting B cells that produce cryoglobulins; and (iii) nonspecific immunosuppressive therapy targeting inflammatory cells at the glomerular level.

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Table 18.2 Prospective randomized clinical trials and controlled (or cross-over) clinical trials for the treatment of MPGN.

Authors (reference year)	Patients, *n*	MPGN, type	Study, design	Study, details	Results
Tiller et al. (1981)	39 (adults)	I and II	RCT	Cyclophospha-mide, warfarin, dypiridamole vs. placebo	Not conclusive
Zimmerman et al. (1983)	18 (adults)	I	Prospective, cross-over	Warfarin and dipyridamole vs. no therapy	Paired analysis: better preservation of kidney function in the treatment year
Donadio et al. (1984)	40 (adults)	I	Prospective, randomized, double-blind, placebo-controlled study	Dypiridamole and aspirin vs. placebo	Slower deterioration of kidney function
Mota-Hernandez et al. (1985)	18 (children)	I	Double-blind controlled	Prednisone vs. placebo	Prednisone reduces ESRD
Cattran et al. (1985)	59 (adults and children)	I and II	RCT	Cyclophospha-mide, coumadin, dypiridamole vs. no therapy	Treatment ineffective in altering the natural history of type I MPGN
Tarshish et al. (1992)	80 (children)	I, II, and III	Randomized, double-blinded, placebo-controlled clinical trial	Prednisone or lactose was given every other day as a single morning dose	Renal survival rate was better in patients on prednisone than those receiving lactose ($P = 0.07$)
Zauner et al. (1994)	18 (adults)	I and II	RCT	Aspirin and dypiridamole vs. no therapy	Lower proteinuria, no impact on creatinine
Giri et al. (2002)	30 (adults)	I	Comparative study	ACEIs vs. non-ACEIs	ACEIs reduce proteinuria and improve serum creatinine

ACEIs, angiotensin-converting enzyme inhibitors; ESRD, end-stage renal disease; MPGN, membranoproliferative glomerulonephritis; RCT, randomized controlled trial.

Table 18.3 Treatment of idiopathic MPGN with mycophenolate mofetil (adults).

Author (reference year)	Patients, *n*	Age	Drug	Treatment duration (months)	Outcome	Kidney, type
Levin et al. (2002)	1	56	MMF/low-dose steroids	12	Proteinuria and SCr decrease	Native
Choi et al. (2002)	1	78	MMF	11	Proteinuria decrease	Native
Jones et al. (2004)	5	32.1 ± 11.6	MMF/low-dose steroids	6	Proteinuria decrease	Native
Segarra et al. (2007)	15	NA	MMF	12	Partial remission of proteinuria ($n = 8$)	Native
Yuan et al. (2010)	13	NA	MMF/low-dose steroids	12	Proteinuria decrease	Native
Mori et al. (2013)	1	26	MMF/low-dose steroids	NA	Proteinuria decrease	Native
Koratala et al. (2018)	1	22	MMF	2	Proteinuria decrease	Native

MMF, mycophenolate mofetil; MPGN, membranoproliferative glomerulonephritis; SCr, serum creatinine.

The information in the literature regarding the management of HCV-associated MPGN is limited; the incidence of the disease is probably low even if epidemiological studies on this point are lacking. No prospective RCTs to establish evidence-based recommendations to treat MPGN associated with HCV exist. We urgently need this evidence as renal disease is now considered a major cause of morbidity and mortality in mixed cryoglobulinemic vasculitis induced by HCV.

Several clinical studies regarding the antiviral therapy of HCV-associated glomerular disease (including HCV-related MPGN) have been published, some based on IFN [51–53] and others that adopted direct-acting antiviral agents (DAAs) [54, 55]. The evidence generated from these studies suggests that the advent of interferon-free antiviral therapy based on DAAs represents a real advance even in so far "difficult-to-treat" settings such as HCV-induced MPGN

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Table 18.4 Treatment of idiopathic MPGN with alternative drugs (children and adults).

Author (reference year)	Patients, *n*	Age	Drug	Treatment duration	Outcome	Kidney, type
Haddad et al. (2007)	2	8 (7–9)	TAC/low-dose steroids	20 months ($n = 1$) 4 months ($n = 1$)	Complete proteinuria remission	Native
Bagheri et al. (2008)	18	27 ± 9	CsA/low-dose steroids and ACEIs	NA	Complete ($n = 12$) or partial proteinuria remission ($n = 5$)	Native
Sugiura et al. (2011)	1	48	RTX	$375\,mg/m^2 \times 1$	Partial remission of proteinuria	Native
Wallace et al. (2012)	1	60	Imatinib/low-dose steroids	$2 + 10$ months	Proteinuria and SCr decrease	Noninfection-related Cryoglobulinemic MPGN
Dillon et al. (2012)	6	57 ± 19	RTX	$1\,g \times 2$ (days 1 and 15)	Complete ($n = 2$) and partial ($n = 4$) proteinuria reduction	Cryoglobulinemic MPGN ($n = 2$)
Kong et al. (2013)	2	49.5	RTX	$375\,mg/m^2 \times 2$ ($n = 1$) $375\,mg/m^2 \times 1$ ($n = 1$)	Complete ($n = 1$) and partial ($n = 1$) proteinuria reduction	Native
Farooqui et al. (2015)	1	58	RTX	$375\,mg/m^2 \times 2$	Complete remission of proteinuria	Living-unrelated donor kidney transplant
Yango et al. (2019)	1	NA	RTX/plasmapheresis	NA	Proteinuria and SCr decrease	Living donor kidney transplant

ACEIs, angiotensin-converting enzyme inhibitors; CsA, cyclosporine; MPGN, membranoproliferative glomerulonephritis; NA, not applicable; RTX, rituximab; SCr, serum creatinine; TAC, tacrolimus.

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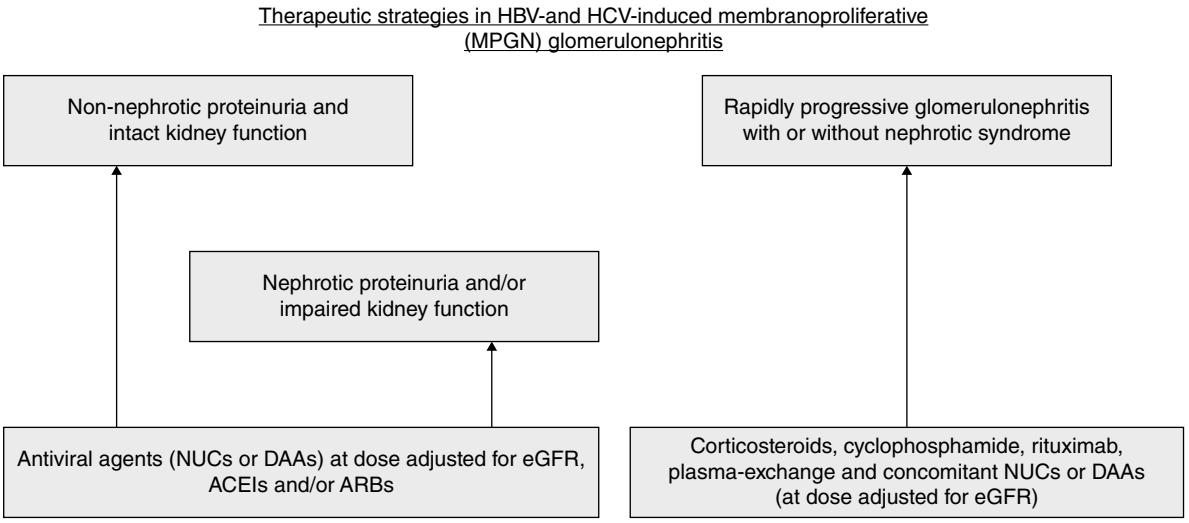

Figure 18.4 Treatment of HBV- and HCV-associated MPGN according to the clinical presentation.

(and other HCV-induced glomerular diseases). These studies have an observational and uncontrolled design; in addition, the size is small. The extensive use of DAAs for the antiviral therapy of HCV in the adult general population will make the frequency of HCV-associated MPGN even more uncommon in the near future.

Some studies regarded the treatment of HCV-associated glomerular disease (including many cases of HCV-associated MPGN); others assessed the antiviral treatment of HCV-associated cryoglobulinemic disease, but the details concerning the cryoglobulinemic glomerulonephritis (including cryoglobulinemic MPGN) were not reported clearly [56]. Of note, the sustained viral response (i.e. the clearance of HCV RNA from serum which persists at least 3 months after completing antiviral therapy with DAAs) is often accompanied by improvement of glomerular abnormalities (reduction of proteinuria, haematuria, and serum creatinine) and this effect has been achieved in the absence of concomitant immunosuppressive therapies. However, clinical improvement after antiviral agents is sometimes incomplete and this is in keeping with the notion that circulating cryoglobulins may be an independent risk factor for clinical nonresponse to antiviral treatments. In addition, remote onset of glomerular disease may be another explanation. In other cases, glomerular and/or cryoglobulinemic disease relapsed over a long follow-up despite sustained virological response (SVR) and it is well known that cryoglobulinemic vasculitis shows an own course, regardless of the presence of trigger agents such as HCV (or HBV). However, the absence of HCV RNA from serum allows the adoption of immunosuppressive therapies with benefits for glomerular changes and no concern on replication of HCV (Figure 18.3).

At the present time the cumulative evidence from the published studies is not satisfactory; clinical studies or anecdotal reports have suggested that IFN-based regimens were provided with low efficacy and high toxicity in patients with HCV-related GN (including HCV-associated MPGN) compared to those with intact kidneys. The evidence from some observational studies reported that the treatment of HCV-associated glomerular disease (including HCV-associated MPGN) with DAAs has given a frequency of SVR of 95–100%, much greater than that obtained with IFN-based therapy (35–50%) [54–56].

As mentioned in these recent series, there were some clinical nonresponders or relapsers despite SVR and this highlights the role of immunosuppressive agents in the management of HCV-associated MPGN (and other HCV-related glomerular diseases). Only preliminary data exist on the immunosuppressive agents, i.e. micophenolate mofetil [57, 58], rituximab [59], or immunomodulatory therapy (low-dose ribavirin) [60] for HCV-related glomerular disease.

C3 Glomerulopathy

The optimal treatment for C3G remains unclear and various approaches have been suggested, at least from a theoretical point of view. C3G was grouped with other forms of MPGN and this hampered the opportunity to make specific recommendations for C3G.

As with any GN, blockade of the RAS remains part of therapy with lipid-lowering therapy.

Patients with mutations involving deficiency of regulatory proteins of the alternative complement pathway may benefit from replacement of factors with plasma therapy.

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Patients might need lifelong plasma therapy. In contrast, plasma therapy is ineffective in patients with mutations of the membrane cofactor protein (MCP, also known as CD46) since it is a membrane-bound protein and replenishing plasma with this protein would not offer protection to the endothelial cells. In patients with gain of function mutations in complement activating proteins (such as factor B or mutant C3 convertase resistant to CFH), plasma therapy may be detrimental since it provides additional substance to activate AP.

Plasma exchange replenishes plasma with deficient proteins, removing autoantibodies or mutant proteins that activate the AP. The response to PE remains short lived and rebound complement activation is noted within 48 hours.

Theoretically, immunosuppressive therapy (based on corticosteroids, MMF, and rituximab) should reduce or eliminate autoantibody production. However, the effectiveness of this approach appears unclear and no RCTs supporting this approach have been made; most of the evidence concerning RTX is based on a few case reports [61–65] (Table 18.5). Treatment of active disease with MMF and corticosteroids has shown promise in two retrospective case series [66–67], but was not found to be effective in a third report regarding patients with more severe baseline kidney disease [68]. A high recurrence of the original disease after solid organ transplant has been noted in patients who are already immunosuppressed [69].

The advances regarding the current classification have coincided with the availability of the first complement inhibitor, eculizumab (EZ), which is a humanized monoclonal antibody directed against C5. EZ binds to the C5 complement protein and inhibits its cleavage into pro-inflammatory and pro-thrombotic C5a and C5b. This binding prevents the generation of the pro-thrombotic and cytolytic terminal complex (C5b-9, membrane attack complex [MAC]). Successful blockade of C5 in C3GN should prevent C5a formation, resulting in lower infiltration of leukocytes. A major side effect of EZ therapy is recurrent meningococcal infections (incidence less than 1%); patients are mandated to receive the meningococcal vaccination in advance to therapy to reduce infection risk.

A small prospective study and a limited number of case series or case reports have shown some efficacy of eculizumab in this disease (Table 18.6) [70–79]. These case reports are clearly subject to publication bias (studies providing positive results are selected for reporting). The introduction of EZ has changed the natural history of aHUS; studies addressing the activity of EZ in patients with C3G have given disparate results, especially compared with results of EZ in patients with aHUS. It appears that treatment with EZ in patients with C3G is beneficial in patients with mild/advanced renal damage, and is able to lower not only proteinuria but also to improve kidney function. It is clear that treatment with EZ requires further assessment in patients with C3G, and prospective studies are those we urgently need. Appropriate candidates to therapy with EZ are patients with C3G who have a relatively short duration of the disease, have shown active inflammatory kidney abnormalities (crescents and endocapillary proliferation), and have reported a recent increase in serum creatinine level and/or proteinuria [79]. The evidence based on pathology is limited and suggests that EZ lowers endo-capillary proliferation and inflammatory cell infiltration in some patients. These findings are in accordance with animal data which showed that anti-C5 therapy effectively targeted the inflammatory

Table 18.5 Rituximab for C_3 glomerulopathy.

Author (reference year)	Patients, *n* (age, years)	Kidney	RTX, protocol	Other therapy	Outcome	Diagnosis
Daina et al. (2012)	1 (22)	Native	375 mg/m^2 ×1	Steroids Eculizumab RAS blockade	No effect of RTX on renal function or proteinuria PR with eculizumab	DDD
Rousset-Rouvière et al. (2014)	1 (8)	Native	375 mg/m^2 ×2	Steroids MMF Eculizumab RAS blockade	Acute renal failure after RTX CR with eculizumab	DDD
Giaime et al. (2015)	1 (34)	Native	700 mg ×4 weekly (repeated after 18 mo)	RAS blockade	Remission of proteinuria with RTX	DDD
Payette et al. (2015)	1 (5)	Native	375 mg/m^2 ×4	Steroids MMF Eculizumab	No effect of RTX on proteinuria PR with eculizumab	DDD

CR, complete response; DDD, dense-deposit disease; MMF, mycophenolate mofetil; PR, partial response; RAS, ; RTX, rituximab.

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Table 18.6 Eculizumab for C_3 glomerulopathy in native and transplant kidneys (adults).

Author (reference year)	Age	C_3G, type	EZ treatment, duration	Outcome	Kidney, type	Response to EZ (histopathology)
McCaughan et al. (2012)	29	DDD ($n = 1$)	10 weeks	SCr improved PCR improved	Graft	NA
Daina et al. (2012)	22	DDD ($n = 1$)	12 months	SCr improved PCR improved	Native	NA
Bomback et al. (2012)	27.2 (20–42)	DDD ($n = 3$) C_3GN ($n = 3$)	12 months	SCr improved ($n = 2$) Proteinuria improved ($n = 1$)	Graft ($n = 3$) Native ($n = 3$)	Improved (3/5) Worsened (2/5)
Gurkan et al. (2013)	21	C_3GN ($n = 1$)	53 weeks	SCr improved PCR improved	Graft	Worsened
Inman et al. (2015)	38	C_3GN (n = 1)	>5 months	SCr improved PCR improved	Native	NA
Welte et al. (2018)	29 (14–59)	C_3GN ($n = 5$) DDD ($n = 2$)	19 (3–28)	SCr improved ($n = 2$) PCR improved ($n = 3$)	Graft ($n = 3$) Native ($n = 4$)	Worsened (2/2)
Sahin et al. (2018)	53	C_3GN ($n = 1$)	9 months	SCR improved PCR improved	Graft	NA
Moog et al. (2018)	59	DDD ($n = 1$)	12 months	SCR improved PCR improved	Graft	Worsened
Garg et al. (2018)	51	C_3GN ($n = 1$)	3 years	SCR improved PCR improved	Graft	Improved
Kaartinen et al. (2018)	37	C_3GN (n = 1)	6 months	Poor response	Graft	Worsened
Le Quintrec et al. (2018)	43 (18–65)	C_3G ($n = 13$)	8 (2–51) months	Global clinical response ($n = 4$) Partial clinical response ($n = 1$) No response ($n = 8$)	Graft ($n = 3$) Native ($n = 4$)	Improved

C3G, C3 glomerulopathy; C3GN, C3 glomerulonephritis; DDD, dense-deposit disease; EZ, eculizumab; NA, not applicable; PCR, urine protein/creatinine ratio; SCr, serum creatinine.

component of C3 glomerulopathy [80]. The current approach to C3G is mostly based on case studies and expert opinion; trial data are currently lacking. Long-term use of EZ is required in this disease due to the inherent risk of recurrence but this hampered by the cost burden (use of EZ for 1 year has been associated with an approximate cost of US$600 000).

The pathophysiology of C3G remains unclear and is probably more complex than that of aHUS. The levels of complement dysregulation at the site of the C3 and C5 convertase have great variability and this could explain the heterogeneity in response to EZ therapy in patients with C3G. Patients with C3G who show important activation of C5 convertase will benefit from therapy with EZ; on the contrary, patients with C3G who have significant dysregulation at the level of C3 convertase will not show dramatic benefit.

Some clinical trials using targeted complement inhibition with novel agents (i.e. compstatin, which is a C3 inhibitory peptide) are under way and promise to change more radically than EZ the management of C3G.

Summary

Recent advances have been made in the last decade regarding the understanding of the multiple pathogenetic pathways of MPGN. This has given us the possibility to expand the therapeutic armamentarium against MPGN. However, at this time there is insufficient high-quality evidence regarding effective and safe therapies for MPGN. Idiopathic or primary immune-complex MPGN is clearly an uncommon condition and an extensive evaluation is required to exclude the etiologies reported above. The low frequency of MPGN could at least partially explain the paucity of controlled trials on this issue.

Adults with idiopathic immune-complex MPGN showing *nephrotic syndrome* and *progressive decline of kidney*

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function should receive an oral course of cyclophosphamide, or MMF, or oral/intravenous corticosteroids. The initial therapy should be limited to less than 6 months (evidence level, 2C).

The management of C3 glomerulopathy is not based on RCTs as the diseases (C3GN and DDD) are very uncommon. Only small case series and case reports have been made. In patients with C3 glomerulopathy who present *mild disease*, i.e. haematuria, low-grade proteinuria (<0.5 g/day), and intact kidney function, management should include RAS blockade with ACEIs and ARBs (evidence level, 2D). Patients with C3G and *moderate or severe renal disease* (greater levels of proteinuria, nephrotic proteinuria, and/or kidney dysfunction) should receive treatment according to the underlying etiology. Plasma exchange, rituximab, steroids, and eculizumab should be considered in patients with C3G where antibody-stimulating AP have been identified (evidence level, 2C). Treatment with EZ allows targeted complement inhibition and has considerably improved the prognosis of some patients with C3G; however, the C5 blockade does not seem to significantly alter the course of the disease in many cases. The therapeutic regimen consisted of 900 mg EZ, given intravenously, weekly for 4 consecutive weeks, and then 1200 mg/2 weeks for 12 months [68]. We need prospective trials or cohort studies to assess the efficacy of EZ and its superiority over conventional approaches (i.e. cyclophosphamide, corticosteroids, and MMF). In patients with C3G due to genetic defects, fresh frozen plasma is indicated to replace the insufficient plasma concentration of CFH or any other related protein. Patients with C3G and *rapidly progressive GN* should receive rescue therapy (pulses of intravenous corticosteroids and oral cyclophosphamide or MMF). Methylprednisolone pulses (0.5–1 g/day) for 3 days followed by oral prednisone (1 mg/kg/day body weight and slow tapering over 2–3 months) and cyclophosphamide. This approach is not specifically targeted to DDD or C3GN (evidence level, 2D).

Patients with HCV-induced MPGN showing *stable kidney function* and/or *non-nephrotic proteinuria* should receive initially antiviral therapy with DAAs. (evidence level, 1B) Patient with HCV-induced MPGN showing *cryoglobulinemic flare*, *nephrotic syndrome*, or *progressive kidney failure* should receive antiviral therapy with DAAs and concomitant immunosuppressive therapy (and/or plasma-exchange) (evidence level, 1B). Rituximab should be considered the first-line immunosuppressive agent in patients with HCV-related MPGN, even in those who do not respond to antiviral therapy (evidence level, 1B).

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19

Autosomal Dominant Polycystic Kidney Disease

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Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is a progressive chronic kidney disease (CKD) that in ~90% of cases has four features: (i) autosomal dominant pattern of inheritance in first-degree relatives; (ii) mutation in one of the causative genes (*PKD1, PKD2* or others); (iii) variable expressivity but complete age-dependent penetrance of multiple renal cysts that fulfill the Pei-Ravine ultrasound criteria; and (iv) variable systemic complications (extra-renal cysts in solid organs, vascular aneurysms, connective tissue defects, such as hernia) [1–11] (Table 19.1).

Epidemiology

Incidence and Prevalence of ADPKD in the General Population

ADPKD occurs uniformly throughout the world. Disease mutations occurred early in modern human evolution. Determining the prevalence of ADPKD is difficult as the condition is clinically silent in up to 50% of patients. The Danish and Olmstead cohort studies (which included autopsy specimens) performed in the 1950s and 1980s, respectively, showed that the lifetime risk in the general population was 1:1000, with an annualized incidence of 2.75 per 100 000 person-years [12, 13]. More recent studies performed in selected geographic areas in the 2010s suggested a lower prevalence (4.76 per 10 000, Modena, Italy [14], 3.96 per 10 000 European Union [15], 5.73 per 10 000, southwest Germany [16]). An analysis performed in 2018 showed that the frequency of high-confidence mutations in *PKD1/PKD2* was 9.3 cases per 10 000 cases in two large population sequencing databases [17]. Taken together, these data indicate that the true incidence of ADPKD in the general population is probably 1:1000 but that the overall incidence of symptomatic ADPKD leading to end-stage kidney disease (ESKD) is approximately 1:2500.

Pathophysiology

ADPKD is due to heterozygous germ-line mutations in *PKD1* (85% of cases, located on chromosome 16p13.3, 46 exon-length), *PKD2* (15%, located on chromosome 4q21, 15 exon-length), or rarely additional genes (<1:1000, such as *GANAB* or *DNAJB11*). Approximately 10% of patients have no mutation detected in either *PKD1* or *PKD2* (no mutation detected). The mutations are inherited in an autosomal dominant manner but occasionally may involve other complex genetic mechanisms (e.g. mosaicism or bi-allelic transmission of *PKD1*). *PKD1* and *PKD2* encode two cellular membrane proteins: polycystin-1 and polycystin-2, respectively. The formation of the kidney cysts starts in early life due to random postnatal reductions in *PKD1* or *PKD2* dose in the principal cells of the collecting duct, as a result of loss of heterozygosity (LOH, "second hits") or other poorly defined stochastic factors. In cohort studies, mutations in *PKD1* are associated with more severe renal disease than *PKD2*, as defined by an earlier onset of ESKD (50–55 vs. 75–80 years old) and twice the number of renal cysts. The clinical phenotype of ADPKD has high intra- and interfamilial heterogeneity due to environmental (epigenetic) mechanisms and modifying genes [1].

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Table 19.1 Treatment of ADPKD.

Treatment	Recommendation	Certainty of evidence	Strength of recommendation
Diagnosis	We recommend confirming diagnosis using the Pei-Ravine ultrasound criteria.	High	Strong
	We recommend genetic testing in selected clinical circumstances and in consultation with a clinical geneticist.	High	Strong [5]
Assessment of renal prognosis	We recommend evaluating factors associated with high risk for ESKD in an individual patient to guide patient education, frequency of clinical follow-up, and treatment.	Moderate	Strong
Genetic counseling	We suggest referral to a clinical geneticist and genetic counselor if detailed advice on family planning and pre-implantation genetic diagnosis is sought by patients and/or if genetic testing is being considered to inform diagnosis.	Low	Weak [5]
Screening at-risk of ADPKD	We recommend screening all first-degree adults at risk of ADPKD with renal ultrasound.	High	Strong
	We suggest that parents be informed of the advantages/disadvantages of screening by renal ultrasound for ADPKD in children <18 years old who are at risk (50%) of ADPKD.	Low	Weak
Fluid intake	We suggest consuming fluids as advised by the treating physician.	Low	Weak [6]
Blood pressure lowering	All patients with ADPKD should receive either an ACEI or ARB for first-line pharmacological treatment of hypertension (>130/80 mmHg) and the stepwise use of a α/β cardio-selective blocker, dihydropyridine calcium channel blocker or a diuretic either as second-line agents or in combination with first-line drugs.	High	Strong [7]
Disease-modifying treatments	We do not recommend the use of somatostatin analogs or target of rapamycin complex 1 inhibitors, and to use shared decision-making regarding the use of vasopressin receptor antagonists in patients with "rapid progression" as defined by a historical decline in the eGFR.	High	Weak [7]
Chronic kidney pain	We suggest that chronic pain is evaluated during clinic visits and that management should be stepwise, involving nonpharmacological and pharmacological treatments, and minimally invasive and invasive therapies.	Low	Weak [8]
Kidney cyst infection	We suggest that suspected renal cyst infection is treated with empirical antibiotic therapy and renal cyst aspiration if refractory to treatment.	Low	Weak
Kidney cyst hemorrhage	We suggest that renal cyst hemorrhage be treated with bed rest and analgesia as first-line treatment, followed by minimally invasive or invasive therapies if bleeding is refractory.	Low	Weak
End-stage kidney disease	We recommend that patients with ESKD be considered for kidney transplantation and evaluated for need for nephrectomy prior to transplantation.	High	High [9]
Polycystic liver disease	We suggest that severe polycystic liver disease (total liver volume >1800 ml/m) is managed by a multidisciplinary team (hepatologist, hepatobiliary surgeon, interventional radiologist, nephrologist).	Low	Weak [10]
Intracranial aneurysm	We recommend that MR angiography or CT (circle of Willis angiography) be used for screening and detection of ICAs in asymptomatic individuals at high risk for an ICA (i.e. a positive family history of SAH/unruptured ICA in at least one first-degree relative with ADPKD or previous SAH/ICA).	Moderate	Weak [11]
	We recommend urgent intracranial imaging in patients who experience a sudden onset of severe headache or neurological symptoms of concern.	Very low	Weak [11]
	We recommend referral to a neurosurgeon if an ICA is detected, and suggest treatment in centers which have expertise in endovascular coiling and microsurgery.	Very low	Weak [11]

GRADE assessment of the certainty of the evidence [12]: High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different* is low. Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different* is moderate. Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different* is high. Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different* is very high. **Substantially different = a large enough difference that it might affect decision-making*.

ACEI, angiotensin converting enzyme inhibitor; ADPKD, autosomal dominant polycystic kidney disease; ARB, angiotensin receptor blocker; CT, computed tomography; eGFR, estimated glomerular filtration rate; ESKD, end-stage renal disease ICA, intracranial aneurysm; MR, magnetic resonance; SAH, subarachnoid hemorrhage.

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The growth of kidney cysts is slow, exponential, and has interindividual variability (~2–10% per year) leading to kidney enlargement by mid-life (mean 1 kg/kidney vs. 0.2 kg/kidney in health). The expanding kidney cysts compress and destroy normal kidney tissue, causing chronic pain, hypertension, and renal impairment. The growth of renal cysts is mediated by chloride-driven fluid secretion (via the cystic fibrosis transmembrane regulator [CFTR] chloride channel) and proliferation (via multiple signal transduction pathways, including TORC1). in vitro arginine vasopressin (AVP) increases intracellular cyclic adenosine monophosphate (cAMP), CFTR-mediated trans-epithelial fluid secretion, and proliferation of cyst-forming renal epithelial (Madin–Darby canine kidney cells [MDCK] cells), implicating it as an important nongenetic factor in exacerbating renal cyst growth during the postnatal period. Thus, disease-modifying treatments to inhibit proliferation (e.g. sirolimus, a TORC1 inhibitor; metformin, an AMP-activated protein kinase [AMPK] inhibitor), "kidney cyst-specific growth factors" (e.g. vasopressin), and other pathways have been investigated in clinical trials [1].

Diagnosis

Renal Ultrasound in Patients with a Positive Family History

We recommend confirming the diagnosis with renal ultrasound using the Pei-Ravine ultrasound criteria in all patients at risk of ADPKD (positive family history of autosomal dominant pattern of inheritance in first-degree family members) (high certainty, strong recommendation) [18, 19]. Renal ultrasound is the preferred imaging modality as it is safe, reliable, inexpensive, and easily accessible. The Pei-Ravine criteria use kidney cyst number according to age (Table 19.2). If the cyst number fails to meet Pei-Ravine criteria ("indeterminate"), a follow-up ultrasound in 1–2 years is suggested [19].

Renal Ultrasound in the Absence of a Family History

In the absence of a positive family history, there are no evidenced-based ultrasound criteria to make a diagnosis of ADPKD but expert opinion is that at least 10 renal cysts in each kidney are required [19–23]. In this situation or if the ultrasound is indeterminate, other supporting evidence from the history, physical examination, and ultrasound features (such as the presence of hepatic cysts and increased kidney size) might provide evidence to support the diagnosis [19].

Genetic Testing

We do not recommend universal genetic testing in all patients with ADPKD using current technologies (high certainty of evidence, strong recommendation) [20] because (i) the results are inconclusive or negative in 10% of patients with typical ADPKD or as high as 50% with a clinical phenotype that is atypical [21]; (ii) genetic testing is 10 times more expensive than kidney ultrasound [18–21]; and (iii) genotyping does not correlate with phenotypic severity. We recommend restricting the use of genetic testing use to specific clinical situations in consultation with a clinical geneticist (high certainty, strong

Table 19.2 Pei-Ravine's criteria for the diagnosis of ADPKD by renal ultrasound[a] [18,19].

Age in years	Positive family history (genotype unknown)	Number of kidney cysts needed to *make* the diagnosis of ADPKD	Number of kidney cysts to *exclude* the diagnosis of ADPKD
15–29	Yes	≥3 (unilateral or bilateral); *PPV = 100%, sensitivity = 81.7%*	Normal ultrasound does not exclude diagnosis
<40	Yes	≥3 (unilateral or bilateral); *PPV = 100%, sensitivity = 82–96%*	Normal ultrasound does not exclude diagnosis
40–59	Yes	≥4 (at least two in each kidney); *PPV = 100%, sensitivity = 90%*	*<2; NPV = 100%, specificity = 98.2%*
≥60	Yes	≥8 (at least four in each kidney); *PPV = 100%, sensitivity = 100%*	<2
Any age[b]	No	≥10 cysts in each kidney with renal enlargement ± hepatic cysts	N/A

AKPKD, autosomal dominant polycystic kidney disease; NPV, negative predictive value; PPV, positive predictive value.
[a] Criteria based on expert opinion.
[b] Criteria based on the use of conventional 3–5 MHz ultrasound probe with cyst size typically being above 1 cm in diameter. CT, MRI, and more sensitive ultrasound probes detect smaller cysts and therefore the above criteria are not applicable to these imaging modalities.
Source: Based on Mai et al. [19].

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recommendation): (i) the exclusion of disease in potential living related kidney donors under the age of 40 years old (as a normal renal ultrasound and computed tomography [CT] scan does not exclude ADPKD in this setting) (Table 19.3); (ii) during pre-implantation genetic diagnosis [24]; and/or (iii) in the evaluation of a patient with an atypical clinical phenotype (i.e. negative family history, equivocal renal imaging, and unusual clinical phenotype, especially in syndromic forms or early-onset disease) [20].

Method of Genetic Testing in ADPKD The gold-standard for genetic testing in ADPKD has been long-range polymerase chain reaction (LR-PCR) amplification followed by Sanger sequencing of all exons. However, this method is labor-intensive and is being superseded by next-generation sequencing (whole-genome sequencing, targeted exome sequencing) [20].

Table 19.4 Risk factors associated with high risk for ESKD.

Clinical factors
Age >35 years old
Family history of ESKD
Age of at least one family member with ESKD <55 years old (suggest mutation in PKD1) (vs. >70 in PKD2)
Onset of hypertension<35 years old
Episode of hematuria <30 years old
Laboratory investigators
Albuminuria
Renal function
• Baseline serum creatinine>92 μmol/l
• Stage 2 CKD by 30 years old, stage 3 by 50 years old or stage 4/5 or ESKD by 55 years old
• Annual rate of decline in eGFR >5 ml/min in 1 year or >2.5 ml/min/year over 5 years
Imaging
Renal length on ultrasound >16.5 cm

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; PKD1, polycystic kidney disease gene-1; PKD2, polycystic kidney disease gene-2.

Prognosis

We recommend evaluating factors associated with high risk for ESKD in an individual patient to guide patient education, frequency of clinical follow-up, and treatment (Table 19.4) (moderate certainty of evidence, strong recommendation). However, the certainty of estimating risk in an individual is low because (i) there is wide clinical heterogeneity in the severity of kidney disease (even within the same family); (ii) the accuracy of current methods to estimate the risk of development of ESKD are poor and based on a limited prospective cohort studies; (iii) disease-specific imaging biomarkers (Ht-TKV by magnetic resonance imaging [MRI]) used in research are not available in clinical practice and statistical prediction models (Mayo Subclassification for TKV) are in the early stages of development and not validated; and (iv) many novel molecular biomarkers (e.g. urinary monocyte chemoattractant protein-1, copeptin) are under investigation, but none has superseded standard methods of clinical history, estimated glomerular filtration rate (eGFR), and imaging.

Clinical History

- *Age:* Patients older than 35 years old at presentation have a 1.7-fold increased risk of developing CKD stage 3A (sensitivity 0.60 and specificity 0.66) [25].
- *Family history:* A three-generation family pedigree is recommended in all ADPKD patients: (i) confirm the autosomal dominant pattern of inheritance; (ii) determine

Table 19.3 Summary of diagnostic tests in ADPKD.

Test	What does it measure?	Comments
Pei-Ravine ultrasound criteria	• Determines the number of renal cysts based on age in a population at 50% risk of having ADPKD • Validated by genetic testing • Simple and cost-effective • May be indeterminate in up to 10% of cases	• Applies only if there is a family history of ADPKD in a first-degree relative • Criteria in the absence of family history are based on expert opinion • Negative ultrasound excludes ADPKD only after the age of 40 (important to recall this fact during live-kidney donor assessment involving family members)
Genetic test	• Provides direct information of the mutation type (*PKD1* vs. *PKD2* vs. no mutation detected or other genes) • May be indeterminate in up to 10–50% of cases depending on the clinical history	• Diagnostic accuracy in enriched populations is 90% but may decline to 50% in atypical or real-world cases • Analysis is expensive, complex, and time-consuming but likely to be more useful as workflow and technological improvements are reported

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the history of ESKD in the family (and age of onset in family members); (iii) identify other family members who are at-risk for ADPKD; and (iv) screen for a family history of intracranial aneurysms (ICAs). Specifically, a family history of onset ESKD ≤58 years or >68 years predicts a mutation in *PKD1* (PPV 100%, sensitivity 75%) or *PKD2* (PPV 100%, sensitivity 78%), respectively [26].

- *Clinical events:* The onset of hypertension or a urological event (episode of cyst hemorrhage, cyst infection, and/or acute flank pain) below 35 years of age is associated with a truncating mutation in *PKD1* and with a worse renal prognosis [27,28].
- *Perinatal history:* Higher birth weight is protective, with every kilogram at birth deferring the age of ESKD onset by 1.7 years [29] (Table 19.5).

Table 19.5 Clinical value of methods used to predict renal prognosis in individual patients.

Prognostic test	Bias	Precision	Benefits	Harms and cost	Value
Clinical information (Age, age of ESKD in family, birth weight)	High	High	Information easy to obtain but has low sensitivity and specificity	Low in harm and cost	Low-moderate
Tests					
Genetic testing (Sanger)	High	High	Identifies the causative mutation (PKD1 PKD2/NMD) but not useful for determining prognosis in an individual patient	Low in harm but very high in cost	Low
Single measurement of total kidney volume at baseline corrected by height	Moderate	High	Estimates the number of kidney cysts and is a disease-specific marker that can identify early risk for ESKD	Not all patients able to do MRI, moderate in cost, and not validated in all population groups (e.g. by ethnicity, country)	Moderate
Single measurement of renal length by ultrasound at baseline	Moderate	Moderate	Estimates the number of kidney cysts and is a disease-specific marker that can identify early risk for ESKD	Low in cost but not validated in all population groups (e.g. by ethnicity, country)	Moderate–high
Serial measurement of Ht-TKV by MRI	Moderate	High	Measures actual rate of kidney cyst growth	Intervals to measure standard; not all patients suitable for MRI, moderate in cost and not validated in all groups	Low
Single eGFR at baseline	Low	Moderate	Estimates GFR but not a disease-specific marker and does not reflect number of functioning nephrons due to glomerular hyperfiltration	Low in harm and cost	High
Serial eGFR changes	Moderate	Low	Estimates the rate of change in eGFR but insensitive in early stage of disease	Useful for late stage of disease and not validated	Low in stage 1 CKD and moderate-high in CKD stages 2–4
Statistical prediction models					
Mayo subclass (Irazabal) class at baseline	Moderate	High	Estimates the rate of kidney cyst growth based on Ht-TKV and age at the time of the test, and therefore subclassifies groups	Not all patients able to do MRI, moderate in cost and not validated in all populations and for ESKD	Moderate
PRO-PKD score	Moderate	High	Composite score based on clinical events and genetic testing	Genetic testing not performed and not validated in all populations	Low

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; GFR, glomerular filtration rate; Ht-TKV, height-adjusted total kidney volume; MRI, magnetic resonance imaging; NMD, no mutation detected; PKD1, polycystic kidney disease gene-1; PKD2, polycystic kidney disease gene-2; PRO-PKD, predicting renal outcomes in autosomal dominant polycystic kidney disease.

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Investigations

Laboratory and imaging tests. The performance characteristics of tests for renal function (serum creatinine and urea; urine albumin to creatinine ratio) and kidney volume (Ht-TKV by MRI and renal length by ultrasound) to estimate the 8-year risk of developing CKD stage 3a are shown in Table 19.6 [25]. These data are derived from longitudinal follow-up of a prospective cohort of 241 ADPKD patients who had an initial creatinine clearance >70 ml/min aged between 15 and 45 years [25]. In this cohort 30.7% of patients reached the study CKD3A during follow-up period. These data indicate that baseline serum creatinine has similar performance characteristics to kidney size (as determined either by MRI or ultrasound) [30].

eGFR and serum creatinine: The precision of eGFR is strongly correlated with measured glomerular filtration rate (GFR) and predicts the subsequent decline in renal function [31, 32]. The decline in renal function is estimated by the rate of change in eGFR using the CKD-EPI formula in serial measurements. ADPKD patients typically display decades of stable or mildly abnormal GFR until mid to late adulthood [32]. Once abnormal and compared to other forms of CKD, the decline in renal function can be rapid (up to 3–4 ml/min/1.73 m^2) per year depending on kidney enlargement [32].

Lack of validity to define "rapid progressor." The availability of tolvaptan in some regions has forced the use of decline in eGFR to define patients with "rapid" rates of progression [33]. The latter has been defined as the presence of eGFR <90 ml/min/1.73 m^2 with either (i) decline in eGFR of >5 ml/min/1.73 m^2 in 1 year; or (ii) decline in eGFR of >2.5 ml/min/1.73 m^2 per year over 5 years [33]. However, the clinical rationale and effectiveness of this definition to categorize patients in this manner is not supported by long-term outcome data. Alternatively, Blanchette [34] (in a retrospective observational cohort analysis; $n = 8018$), defined rapid progression as if one or more of the following were present: hypertension <35 years old, hematuria <30 year, albuminuria; stage 2 CKD by age 30; stage 3 by age 50, and/or stage 4/5 or ESKD by 55 year (50% vs. 75% 5-year renal survival).

Imaging: Total kidney volume (TKV) by MRI is a disease-specific biomarker useful for evaluating progression in clinical trials of patients with preserved renal function. In contrast, in clinical practice, the value of TKV over annual eGFR measurement in predicting renal prognosis is uncertain. Current evidence is limited to a single longitudinal cohort study where baseline height corrected-TKV>650 ml/m only marginally outperformed the baseline serum creatinine (97 μmmol/L) in predicting CKD stage 3A over 8 years (Table 19.6) [30]. However, as MRI is not reimbursed in many countries, longitudinal kidney length on ultrasound provides a simple parameter that can be used in clinical practice. In this regard, in the same cohort study a kidney length greater than 16.5 cm on renal ultrasound had a similar performance to Ht-TKV in predicting the development of 8-year risk of CKD stage 3A (Table 19.6) [30].

Statistical Prediction Models

Currently two models have been developed: (i) the Irazabal (Mayo) subclassification [35] and the PRO-PKD score [28] (Tables 19.7 and 19.8). The Mayo subclassification might be useful for prognostic enrichment in clinical trials. However, in clinical practice, barriers exist to applying both of these

Table 19.7 Irazabal (Mayo) subclassification [35].

Scoring method (Ht-TKV divided by age − 150 ml) × 100		
Mayo subclass	**Estimated kidney growth rates/ year (%)**	**Risk for ESKD**
A	<1.5	Low
B	1.5–3.0	Intermediate
C	3.0–4.5	Intermediate
D	4.5%–6.0	High
E	>6.0	High

ESKD, Ht-TKV
Source: Based on Irazabal [35].

Table 19.6 Eight-year risk of developing CKD stage 3a.

Variable	AUC (95% CI)	Sensitivity	Specificity	Cut-off point	LR of positive test
Serum Cr	0.75 (0.67–0.82)	0.58	0.81	97 μmol/l	3.05
Serum urea	0.76 (0.70–0.83)	0.63	0.79	5.7 mmol/l	3.0
Urine albumin	0.70 (0.61–0.78)	0.66	0.67	30 mg/day	2.0
Ht-TKV (MRI)	0.84 (0.79–0.90)	0.74	0.70	600 ml/m	2.96
Kidney length (US)	0.87	0.795	0.732	630 ml/m	2.97

AUC, area under the curve; Cr, HtTKV, LR, likelihood ratio; MRI, magnetic resonance imaging.
Source: Adapted from [25, 30].

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Table 19.8 PRO-PKD score [28].

Scoring method		Score interpretation		
Parameter	**Score**	**Score**	**Risk for ESKD <60 years**	**Median age of ESKD**
Male	1 point	0–3	Low (NPV = 81.4%)	70.6
Hypertension <35 years old	2 points	4–6	Intermediate	56.9
First urologic event <35 years old	2 points	7–9	High (PPV = 90.9%)	49
Genotype				
• PKD2 mutation	0 point			
• PKD1 mutation (non-truncating)	2 point			
• PKD1 mutation (truncating)	4 points			

ESKD, end-stage kidney disease; NPV, negative predictive value; PKD1, polycystic kidney disease gene-1; PKD2, polycystic kidney disease gene-2; PPV, positive predictive value; PRO-PKD, predicting renal outcomes in autosomal dominant polycystic kidney disease.
Source: Cornec-Le Gall [28].

models as (i) the tests incorporated in the models (Ht-TKV for Mayo subclassification and genetic testing for PRO-PKD) are not part of routine clinical practice; and (ii) the models have not been validated prospectively for the development of ESKD or in real-world populations.

Treatment

Figure 19.1 provides an overview of the management approach in a patient with ADPKD. The key goals of care in ADPKD are to preserve quality of life (QoL) and normal life expectancy by (i) reducing the lifetime risk of ESKD; (ii) preventing and/or minimizing cardiovascular disease; and (iii) treating and managing extrarenal disease manifestations. The management of ADPKD should be "patient-centered" (i.e. care in which patients and their families are active partners in decision-making by being provided with clear and accurate knowledge regarding their situation) and "personalized" (i.e. "a disciplined approach to delivering care that responds to patients' circumstances, capabilities, and preferences").

Genetic and Psychosocial Care

The provision of coordinated genetic, medical, and psychosocial care should be the overarching goal of care [27]. Due to the systemic nature of disease manifestations, multidisciplinary care is typical for most patients with ADPKD and is tailored according to local health services, but the optimal model of delivery is not known.

Genetic Care

- *Genetic counseling:* As there is high intra- and interindividual variability in ADPKD, it is important that all patients receive education that is individualized to suit their circumstances. The counseling should include a discussion on the mode of inheritance (as well as communicating this to at-risk family members); the role, indication, and interpretation of diagnostic testing; information regarding the natural history, prognosis, and treatment; and options regarding family planning and prenatal testing options (including preimplantation genetic diagnosis). Referral to specialized genetic services and a genetic counselor can be offered to enhance the care, especially if molecular genetic testing is considered and/or family planning anticipated (such as preimplantation genetic diagnosis low certainty, weak recommendation). Patients should be informed about patient support organizations for PKD as well as centers where clinical trials in PKD or other novel treatments are being conducted.
- *Screening of adults and children at-risk of ADPKD:* Screening of first-degree adult relatives is recommended [36]. Renal ultrasound is the first-line screening test, and patients should receive the appropriate counseling regarding the advantages and disadvantages prior to performing predictive testing (high certainty, strong recommendation) (Table 19.9). The optimal approach for screening asymptomatic at-risk children (<18 years of age) is unknown but the decision should be individualized and considered with parental discussion (low certainty, weak recommendation) [37]. The historical view has been to defer screening children until adulthood but this view must be challenged [37, 38] due to the following emerging evidence: (i) at least one renal cyst may be detected in up to 80% of children who are at-risk of ADPKD [39]; (ii) hypertension is present in up to one-third of children [39] and a systematic review showed that ~8% reduced have renal function

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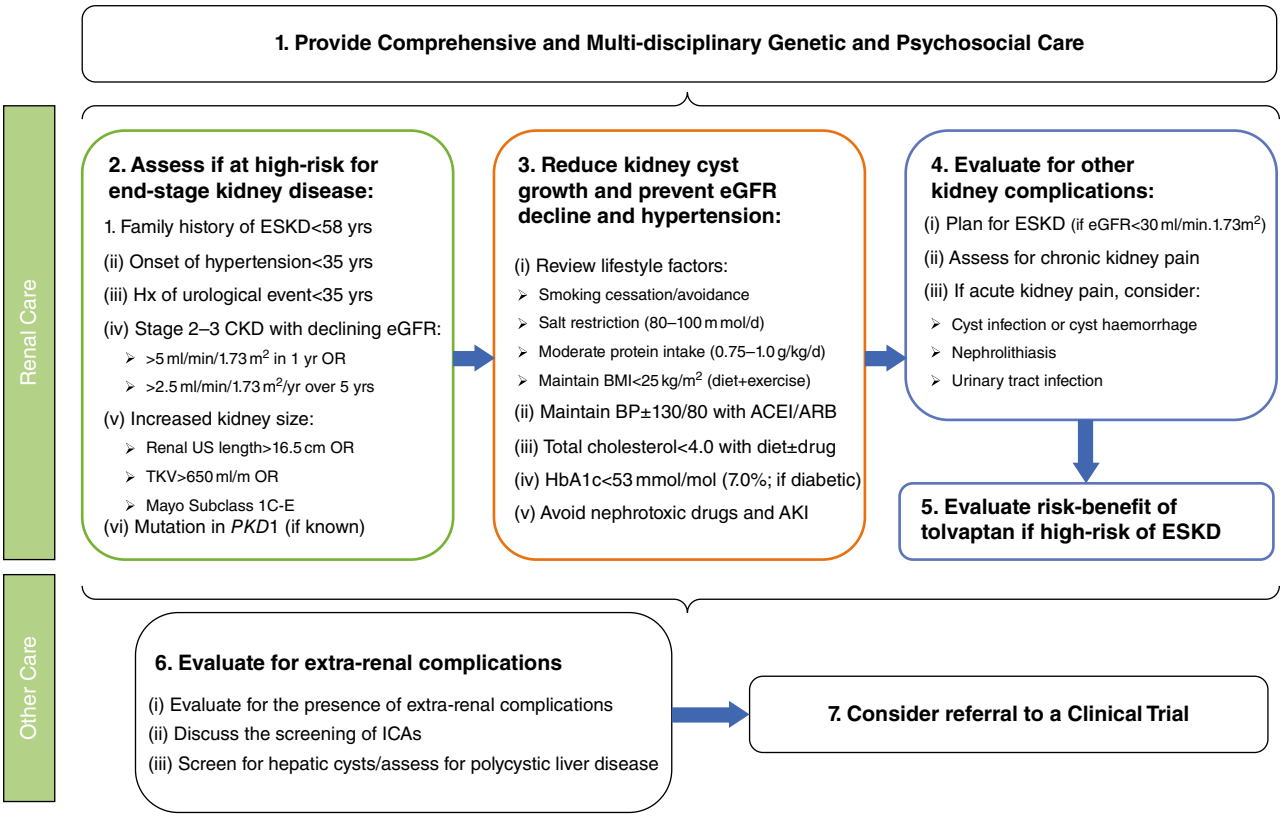

Figure 19.1 Overview of the treatment of ADPKD. *Source:* Adapted and modified from Rangan et al. [1].

Table 19.9 Benefits and disadvantages of screening adults at-risk for ADPKD.

Benefits of screening adults at-risk for ADPKD	Disadvantages of screening adults at-risk for ADPKD
Reduces uncertainty and anxiety	False negative result requiring re-testing
Diagnosis permits early treatment of complications	Financial discrimination
Permits decisions regarding lifestyle and employment	Employment discrimination
Permits discussions on reproductive options	Changes in social and family interactions
Allows family members to be informed	Psychological impact of diagnosis
Identify potential unaffected living-related kidney donors	

[40]; and (iii) subclinical manifestations of ADPKD begins in childhood, and early detection and treatment may slow renal cyst growth [41] with the potential to eliminate the lifetime risk of ESKD and other extrarenal manifestations in high-risk families [22] [24].

- *Family planning and preimplantation genetic diagnosis (PGD):* Couples with ADPKD should be informed of the pattern of inheritance and risks during pregnancy. The perinatal risks of pregnancy to a mother with ADPKD are dependent on the level of kidney dysfunction and/or hypertension. Young families with ADPKD are increasingly interested in PGD. In a survey of 96 UK patients with ADPKD, the majority (>95%) were concerned about the risk of genetic transmission [42] and most (>80%) would consider using PGD [42]. PGD involves in vitro fertilization as well as genetic testing and therefore id a costly procedure, but it is considered an option by patients with ADPKD with a family history of severe disease [24]. The application of PGD requires expert genetic counseling given the large phenotypic variability in ADPKD and complexities in genetic testing. Patients should be referred to specialist centers with previous experience and expertise in in vitro fertilization and molecular diagnostics [24]. The long-term outcome of PGD in ADPKD is unknown and will be informed by an ongoing observational cohort study underway in China (ESPERANCE trial; NCT02948179).

Acute and Chronic Psychological Care

The prevalence of psychological issues (anxiety, depression, denial, anger) in ADPKD is higher than in to the general population [27, 43]. Acute psychological symptoms

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are worst at the time of diagnosis when it comes as a "shock" to patients (some patients describe being told the diagnosis as a receiving a "bomb") [27, 43, 44]. The origins of emotional distress in ADPKD are complex but include the hereditary nature of the disease (with patients calling it an "evil heritage" and experiencing guilt from transmitting the disease to future generations), the uncertainty of future prognosis regarding the kidney disease, chronic pain and lack of effective treatment options, worry about financial factors (future employment status and eligibility for life insurance), impact on family planning, and the changes in body image due to kidney and liver enlargement [45–47]. Psychological factors may negatively influence treatment adherence due to a sense of helplessness and denial. The evidence for psychological care in ADPKD is of low certainty but strongly recommended and includes (i) performing an initial evaluation using screening questions; (ii) determining the severity; and (iii) initiating appropriate management [48, 49]. The goal of care is to recognize and minimize psychological morbidity, and foster patient empowerment and self-motivation [50].

First-line Treatments to Prevent and/or Minimize Renal and Cardiovascular Disease

All patients with ADPKD should receive first-line (or primary) treatment (dietary salt minimization, optimal caloric energy intake) [51], treatment of hypertension with either angiotensin converting enzyme (ACE) or angiotensin receptor blocker (ARB), and avoidance of acute renal injury by minimizing exposure to nephrotoxins (low certainty evidence, strong recommendation). In patients with low to moderate risk of renal disease progression (which may be up to 50-75% of patients) first-line interventions may curtail the lifetime development of ESKD and cardiovascular morbidity if effectively implemented in young adults soon after diagnosis [52].

Diet Modification

Dietary salt restriction: In the HALT-PKD trial, each 18 mEq increase in averaged urinary sodium excretion was associated with a 0.43% per year rise in ht-TKV in patients with eGFR>60 ml/min/1.73 m^2 and with a faster decline in renal function (−0.09 ml/min/1.73 m^2) in patients with eGFR between 25 and 60 ml/min/1.73 m^2 [53]. In addition, in a small randomized controlled trial (RCT) ($n = 34$) of 2 weeks in duration in ADPKD patients with eGFR>60 ml/min/1.73 m^2, an ~30% reduction in urinary sodium intake (as determined by 24-hour urine sodium from ~3 to ~2 g/day) together with an ~40% increase in fluid intake caused a small but signification reduction in serum copeptin (~1 pmol/l) (a surrogate marker of AVP) [54].

Dietary protein intake: A subgroup analysis of ADPKD patients ($n = 141$, Study A; GFR between 25 and 55 ml/min1/1.73 m^2) in the Modification of Renal Disease study showed that a low protein diet (≤0.6 g protein/kg/day) compared to usual protein intake (1.3 g protein/kg/day) did not alter the decline in renal function (5.9 ml/min/year) [55]. Current evidence does not support any specific dietary protein intake for patients with ADPKD beyond standard recommendations in CKD (no recommendation).

Fluid Intake

We suggest consuming fluids whenever and in whatever volume desired or as advised by the treating physician (low certainty of evidence, weak recommendation). The volume of fluid that patients with ADPKD "should" drink is a topical question that has been asked by both nephrologists and patients. It has been hypothesized that maintaining a fluid intake of ~3 l per day may reduce the progression of renal cyst growth in ADPKD by suppressing AVP release [56]. However, there is no high-level evidence to support this as a clinical recommendation [6]. Furthermore, the volume of fluid required to suppress AVP is also likely to vary because it is dependent on the amount of dietary solute intake that a patient consumes [56]. To date, the evidence for the hypothesis is limited and based on short-term studies (less than 2 months in duration) which show that it is possible to reduce serum copeptin at consumption volumes that were tolerable to patients. However, the long-term efficacy (on renal function decline and renal cyst growth), safety, and feasibility of this approach are not known. The only available long-term data in humans is a small nonrandomized observational cohort study ($n = 33$) which showed that the progression of TKV or decline in eGFR in patients who drank 2.5–3.0 l per day was not different to those who consumed lower amounts over a 1-year period [57]. This study was nonrandomized, of insufficient duration and power as well as being an observation cohort design, therefore further data are needed [6]. Caffeine intake is not contraindicated in ADPKD patients (strong recommendation, low certainty evidence) [6].

Blood Pressure Control, Vascular Dysfunction, and Cardiovascular Disease

Blood pressure lowering: Angiotensin converting enzyme inhibitors or angiotensin II receptor blockers are preferred first-line agents for blood pressure control in (high certainty evidence, strong recommendation) [7]. There is limited evidence to guide second-line treatment choice (alone if intolerant to angiotensin converting enzyme inhibitor or in combination) but the stepwise use of a cardioselective blocker dihydropyridine calcium channel blocker, and/or

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or a diuretic is suggested [2]. The KDIGO Controversy Conference on ADPKD suggested a target blood pressure (BP) of ≤130/80 mmHg in patients with macroalbuminuria (≥25 mg/mmol in males and ≥35 mg/mmol in females) or ≤140/90 mmHg if no macroalbuminuria for ADPKD patients [3]. The HALT-PKD trial showed that a target BP of 95/60 to 110/75 mmHg (vs. 120/70 to 130/80) was associated with a small (1.1% per year) but significant reduction in TKV in young ADPKD patients (15–49 years old with eGFR>1.73 m^2) over an 8-year period. This was associated with a 16% increase in dizziness and light-headedness in the low BP target group. Based on this data, the KHA-CARI ADPKD Guidelines suggest a BP target of at least ≤130/80 mmHg, and that a lower target BP could be considered in selected patients [2, 7].

Cardiac manifestations: The prevalence of cardiac valvular abnormalities (especially mitral valve prolapse/incompetence) and cardiomyopathy are increased in ADPKD [58, 59]. The incidence of left ventricular hypertrophy and valvular calcification increases as renal function declines [59]. However, echocardiography is not recommended unless physical examination is abnormal [2].

Intracranial aneurysms

- *Screening:* We recommend that magnetic resonance angiography or CT (circle of Willis angiography) is used for the screening of ICAs in asymptomatic individuals at high risk for an ICA (moderate certainty of evidence, weak recommendation). However, the decision to perform universal/systematic screening (i.e. to screen everyone with ADPKD at diagnosis) or to perform targeted screening for of those with risk factors (i.e. screen those at high-risk, family history of SAH, presence of neurological symptoms, prior to major surgical procedures) is controversial [60], and this likely explains the higher than expected screening rate in ADPKD patients (~30% undergo screening for ICAs within 2 years of diagnosis of ADPKD) [61]. In this regard, a recent cohort analysis of French patients suggested that screening should be systematic rather than targeted [62]. Interestingly, clinical practice guidelines led by nephrologists recommend performing targeted screening for ICAs whereas professionals from the stroke community favor a universal approach [11, 63]. In counseling patients, the risks and benefits of screening should be carefully discussed, noting that when positive, small aneurysms of the anterior circulation have a low risk of rupture [64]. Overall, complications related to the treatment of unruptured aneurysms may be as high as 15.6% [64]. Cerebral CT angiogram with low-dose contrast or cerebral magnetic resonance angiography is the standard screening method [11].
- *Repeat screening*: Follow-up interval screening is recommended only in patients with a family history of ICA or subarachnoid hemorrhage, or those with previous ICA or rupture, at intervals between 2 and 5 years, or according to risk factors such as hypertension, smoking, "high-risk" occupation or prior to major elective surgery [3]. The incidence of de novo aneurysms is 1.4% patient/year [64]. Repeat interval screening in low-risk asymptomatic patients with a negative initial scan is not recommended (low certainty of evidence, weak recommendation) [3].

Serum cholesterol and lipid-lowering drugs: We suggest lipid-lowering drugs are prescribed to prevent cardiovascular death based on evidence recommendations in CKD rather than to specifically reduce kidney cyst growth (low certainty of evidence, weak recommendation). In a study of 110 pediatric ADPKD patients (8–22 years), pravastatin mildly attenuated the increase in TKV over 3 years (21% vs. 30% from baseline, $P = 0.02$) independent of serum cholesterol [41], but this was not confirmed in a post hoc analysis of the HALT trial [65].

Physical Activity

Patients should be educated that the risk of renal cyst hemorrhage is increased if the kidney volume is high (e.g. if the longitudinal length is >15–16 cm) and these patients should preferably avoid high-risk contact sports (e.g. boxing, rugby, American football) (low certainty, weak recommendation).

Avoidance of Acute Kidney Injury

ADPKD patients should avoid or minimize their exposure to nephrotoxins (NSAIDs, aminoglycosides, radiocontrast) or procedures that increase the risk of acute kidney injury as it may increase the risk of renal cyst growth (low certainty of evidence, strong recommendation) [66] (Table 19.10).

Disease-modifying Treatments to Prevent and/or Minimize Renal Disease

Disease-modifying treatments may be defined as those for use in selected patients at high risk for ESKD (possibly ~25% of patients) and/or who exhibit features of rapid progression (e.g. "rapid progressor" or other prognostic factors) despite receiving maximal first-line management. The high likelihood of adverse events and/or low uncertainty of evidence are reasons for their exclusion as first-line treatments.

Vasopressin receptor antagonists in patients at high risk for progression of ESKD: The current evidence based on two RCTs does not support the routine use vasopressin

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Table 19.10 Summary of TEMPO 3:4 and REPRISE RCTs [23, 67].

Name	Study population	Study design	*n*	Primary endpoint	Secondary endpoint	Adverse events
TEMPO 3:4	18–50 years old TKV > 750 ml eGFR>60 ml/min	3 years Phase 3 double-blind, placebo (2:1), multicenter	1445	TKV: increase 2.8%/year in the tolvaptan group vs. 5.5%/year in the placebo	Slower decline in kidney function (reciprocal of the serum creatinine level, −2.61 (mg per milliliter)/year vs. -3.81 (mg per milliliter)/year; $P < 0.001$); lower rates of worsening kidney function (2 vs. 5 events per 100 person-year, $P < 0.001$) and kidney pain (5 vs. 7 events per 100 person-years of follow-up $P = 0.007$)	Tolvaptan associated with aquaresis and hepatic and higher discontinuation rate (23% vs. 14% in the placebo group)
REPRISE	18–55 years old (eGFR 25–65 ml/min/1.73 m^2) and 56–65 (eGFR 25–44 ml/min/1.73 m^2), and ability to tolerate tolvaptan after an 8-week pre-randomization period which included sequential placebo and tolvaptan run-in phases	1 year, phase 3, randomized withdrawal, multicenter, placebo-controlled, double-blind trial (1:1)	1370	Change from baseline in the estimated GFR was −2.34 ml per minute per 1.73 m in the tolvaptan vs. −3.61 ml per minute per 1.73 m in the placebo; $P < 0.001$		Reversible increases in the ALT (to >3 times normal range) 5.6% in tolvaptan group vs. 1.2% in the placebo group

Sources: Torres et al. [23, 67].

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receptor antagonists in ADPKD and to use shared decision-making with patients if there is "rapid progression" as defined by a historical decline in the eGFR. [23, 67]. Tolvaptan is a specific vasopressin receptor antagonist that inhibits the binding of AVP at the V_2 receptor (a G_S-protein-coupled receptor) of the cortical collecting duct. In two RCTs, treatment with tolvaptan reduced the rate of decline in eGFR by approximately 1ml/min/1.73m^2/year compared to placebo [23, 67], but the limitations of this data should be considered: (i) the effect size on eGFR was small and apparent only after discontinuation, suggesting a role for hemodynamic and other cofounding factors [68]; and (ii) the long-term effect of tolvaptan on preventing ESKD is assumed and evidence is lacking [68]. In addition, mechanistic questions remain: (i) preclinical studies in *pck* rats suggest that both increased water intake and vasopressin receptor antagonist could have similar efficacy on reducing the kidney to body weight ratio by ~30% [69, 70]; and (ii) in vitro studies support a direct role for inhibition of AVP on renal cyst growth, but it is not known if human renal cysts express V_2 receptor.

The main adverse effects of tolvaptan are aquaresis (mean 5–7 l per day at maximal dose) and 5% of patients may develop reversible drug-induced liver injury. Thus, patients receiving tolvaptan must have liver function tests monitored every 1-3 months while on therapy (low certainty of evidence, strong recommendation).

Somatostatin analogs (octreotide, lanreotide): Somatostatin is a neuropeptide produced by gastrointestinal-derived delta-cells that attenuates intestinal motility, absorption, and proliferation [71, 72]. In humans, the ALADIN study (an RCT of 75 patients) showed that oectroetide reduced the increase in TKV at 1 year but not at 3 years compared to no treatment [71, 72]. The DIPAK-1 study which was a 2.5-year RCT comparing lanreotide + standard care (120 mg SC 4 weekly, $n = 153$) with standard care. The results showed that lanreotide did not alter the decline in eGFR (−3.56 vs. −3.46 ml/min/1.73 m^2 per year) but reduced the rate of increase in TKV (4.2% vs. 5.6%) [71, 72]. These data as well as the high risk of gastrointestinal side-effects do not support the use of somatostatin analogs in ADPKD.

TORC1 inhibitors (everolimus, sirolimus): Animal studies conclusively demonstrated that TORC1 inhibitors suppress the proliferation of cystic epithelial cells and reduce renal cyst growth. However, two clinical trials did not confirm the same efficacy in humans [73]. This disparity could be explained by: patient dropouts due to side effects (mouth ulcers), insufficient drug delivered to target tissue, and trial design, as therapy was initiated when kidneys had reached their near-maximal volume [73].

Kidney Pain

Chronic pain (>4–6 weeks in duration): The optimal management of chronic kidney pain is not certain [8]. Mild diffuse discomfort in the loin, abdomen, or lower back, present on most days, is common and reported by 60% of patients with "large" kidneys due to their physical effect in the abdominal cavity and pressure on the lower lumbar spine. In a cross-sectional analysis of the HALT study cohort ($n = 1043$) back pain was reported in ~50% of patients and was unrelated to kidney volume when the eGFR was greater than 60 ml/min/1.73 m^2 (unless the Ht-TKV exceeded 1000 ml/m) whereas patients with eGFR<60 were more likely to report abdominal fullness and pain that was disabling. The DIPAK cohort analysis ($n = 309$) showed that up to 30% of patients have associated gastrointestinal symptoms (such as heartburn, nausea, vomiting, and early satiety) due to combined kidney and liver volume. In a systematic review of patient perspectives on living with ADPKD, renal pain was described as volatile and incapacitating, which disrupted daily living and impaired ability to establish long-term life goals [47]. Hence, screening for chronic pain should be routine during all clinic visits. There is no high-level evidence to recommend the optimal approach for managing chronic pain. However, in refractory cases, a stepwise approach consisting of nonpharmacological (behavioral modification, physiotherapy, ice/heating pads,) and pharmacological (three-step analgesic ladder) treatments followed by minimally invasive (nerve block) and invasive (cyst aspiration, cyst fenestration, nephrectomy/hepatectomy) therapies is suggested (low certainty of evidence, weak recommendation) [74, 75]. A nonrandomized single-center study showed that a multidisciplinary sequential protocol involving nerve block can relieve pain in up to 80% of patients ($n = 60$) with chronic refractory pain [76].

Acute pain: The incidence of acute pain in ADPKD is less common than chronic pain, and data from the TEMPO 3:4 study suggested an average incidence of seven episodes per 100 years. The sudden onset of acute pain requires evaluation with history, physical examination, and renal imaging (generally by CT). The differential diagnosis includes:

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- *Kidney cyst hemorrhage and rupture*: We suggest that renal cyst hemorrhage be treated with bed rest and analgesia as first-line treatment, followed by minimally invasive or invasive therapies if bleeding is refractory (low certainty of evidence, weak recommendation). Kidney cyst hemorrhage is characterized by sudden onset of sharp localized and unilateral abdominal pain either secondary to contact sports, blunt trauma or may be spontaneous (as cysts are surrounded by neoangiogenesis). In most cases (~80%) cyst hemorrhage bleed into the urinary collecting system causes macroscopic hematuria, and less commonly bleeding is retroperitoneal. The risk of cyst hemorrhage increases with kidney size, especially when kidney length exceeds 15 cm [77]. Bleeding into the collecting system tends to self-resolve, with symptomatic episodes lasting 3–5 days, and management entails bed rest, increased fluid intake, and analgesia. Rarely, selective renal artery embolization is required if retroperitoneal bleeding is refractory or catheter irrigation is required if there is ureteric clot obstruction [78].
- *Nephrolithiasis*: Kidney stones occur in ~30% of ADPKD patients (2-fold higher than the general population) and are usually composed of uric acid or calcium oxalate [79]. They occur because of reduced citrate excretion (an inhibitor of stone formation) and altered tubular urine flow. Clinical features resemble classical renal colic with or without macroscopic hematuria and urological management is the same as in the general population [79].
- *Infection*: Urinary tract infections (UTIs) (upper: pyelonephritis; lower: cystitis, urethritis) occur at least once in ~30–50% of ADPKD patients. The characteristic features are an acute onset of unilateral renal pain, associated with fever, chills, and rigors, and/or macroscopic hematuria with a positive urine culture and pyuria (mostly gram-negative enteric organisms). The mechanisms and management of ADPKD-associated UTI are the same as for the general population. By comparison, an infected cyst (either kidney or hepatic) has a subacute onset, nonspecific symptoms, low-grade fever, and evidence of systemic inflammation (elevated white cell count, C-reactive protein). The urine culture is negative and there may be acute tenderness corresponding to the location of the infected cyst. Features on a CT scan that favor cyst infection (vs. hemorrhage) include increase in cyst wall thickness or rarely the presence of gas within a cyst. There are no evidence-based guidelines for the optimal management of cyst infection. Microbiological confirmation can be difficult, as the urine culture is often negative. Occasionally, CT-guided aspiration of an infected cyst is required if antibiotic refractory. Positron emission tomography can be used as second-line investigation if the diagnosis is uncertain but has low specificity and is expensive. Suspected cyst infection should be treated with lipid- and cyst-permeable antibiotics (e.g. norfloxacin or co-trimoxazole) for an extended duration (4–8 weeks). A systematic review found that risk factors for failure of initial therapy (~39%) were large cysts (diameter >5 cm), ESKD, and atypical organisms [80]. Safety data from the DIPAK trial show that lanreotide is associated with higher risk of hepatic cyst infection for reasons not understood.
- *Effect of tolvaptan on acute pain episodes:* A post hoc analysis of the TEMPO 3:4 study showed that tolvaptan use was associated with a reduced incidence kidney pain events when compared to placebo (10.1% vs. 16.8%, $P < 0.001$) [67]. This effect is largely due to a decrease in acute pain secondary to urinary tract infection, kidney stones, and hematuria, and it is not known if prescribed water intake could also be similar.

Management of Extrarenal Complications

The frequency of extrarenal manifestations is shown in Table 19.11. Psychological morbidity (as discussed earlier) followed by the cardiovascular and gastrointestinal systems are the most commonly affected extra-renal areas. Patients with ADPKD were historically suspected to have an increased incidence of malignancy, but data to support this hypothesis is inconsistent.

Hepatic Cysts and Polycystic Liver Disease

Liver cysts and hepatomegaly occur in up to 80% of patients, but generally remain asymptomatic, with normal liver function tests in ~95% of patients [1, 10]. Approximately 5% of patients develop severe polycystic liver disease (PLD, defined as a height-corrected liver volume >1800 ml/m) predominantly (~80%) in females. The increased risk in females is associated with a history of multiple pregnancies and exposure to hormone replacement therapy, suggesting a causative link to estrogen exposure. In these cases, we suggest that severe PLD be managed by a multidisciplinary team (hepatologist, hepatobiliary surgeon, interventional radiologist, nephrologist; low certainty of evidence, weak recommendation). Short-term clinical trials suggest that somatostatin analogs (octreotide, lanreotide, pasiretoide) reduce symptoms of PLD with a small effect on reducing hepatic cyst growth rate, but long-term outcomes are not known. Rarely, liver transplantation (due to abdominal distension and portal hypertension) is required in severe PKD [1, 10].

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Table 19.11 Frequency of extrarenal manifestations of ADPKD.

	Frequency of patients
Psychological issues	
Anxiety, depression, anger and denial	High
Cardiovascular system	
Cardiac valve abnormalities (mitral valve prolapse)	25%
Hypertension	80–100%
Left ventricular hypertrophy	20–40%
Gastrointestinal system	
Liver cysts	94% >35 years old
Diverticular disease	50–83% in ESKD patients
Hernia	45%
Pancreatic cysts	9–26%
Splenic cysts	2.7%
Choledochal cysts	Rare
Common bile duct dilation	40%
Neurological	
Intracranial aneurysms	9–12%
Arachnoid cysts	8–12%
Spinal meningeal cysts	1.7%
Other organ complications	
Seminal vesicle cysts	40%
Bronchiectasis	37%
Thyroid cysts	Not clearly defined
Risk of malignancy	Controversial, not defined

Management of ESKD in ADPKD

Late-stage 4–5 CKD should be managed as for other types of CKD [9]. Either peritoneal dialysis or hemodialysis are appropriate treatment options to manage ESKD. A recent meta-analysis ($n = 14\,673$) showed that peritoneal dialysis-related complications (technique failure, peritonitis, hernia) in ADPKD patients were similar to those in non-ADPKD patients [81]. As for other types of CKD, kidney transplantation is the preferred modality for the management of ESKD and patients should be evaluated for need for nephrectomy prior to transplantation (high certainty of evidence, strong recommendation). Transplantation may be associated with a ~2-fold increased risk for developing new-onset diabetes compared to other causes of CKD [9].

Conclusion

At present there is minimal evidence that treatment with disease-modifying agents (such as vasopressin receptor antagonists) improves outcomes in ADPKD due to uncertainty regarding efficacy, absence of patient-centered endpoints, and the high risk of significant risk adverse events. On the other hand, it is possible that first-line treatments (as described in this chapter), if instituted consistently in early life, could reduce lifetime risk of ESKD in moderate- to low-risk patients. For high-risk patients, numerous clinical trials are in development and understanding of disease pathogenesis and diagnostics is proceeding at an exponential rate. Furthermore, previously neglected areas of treatment, such as optimal genetic and psychosocial care, ICAs, and polycystic liver disease, are also gaining much deserved attention. The challenge for basic and clinical researchers will be to discover, select, and recommend the most promising interventions that have acceptable side effects (given that they might need to be taken for decades) using the most efficient methods in clinical trial design.

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Urinary Tract Infection

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Introduction

Urinary tract infection is one of the most common bacterial infections around the globe, and is an important cause of morbidity, hospitalization, and antibiotic resistance. Urinary tract infection can be upper or lower; lower urinary tract infection refers to infection of the bladder (or cystitis). Asymptomatic bacteriuria refers to the presence of $>10^5$ colony-forming units in the urine without physical signs of infection. Uncomplicated lower urinary tract infection is usually a self-limiting illness. Symptom duration is reduced by treatment with antibiotics to which the infective pathogen is sensitive. Urinary tract infections occur due to predominantly bowel-related organisms, most commonly *Escherichia coli*, while other common bacterial etiologies include *Staphylococcus* and less frequently *Enterobacteriaceae* (*Proteus mirabilis* and *Klebsiella* spp.). Lower urinary tract infection is frequently identified by specific urinary tract symptoms combined with urine dipstick testing, with or without subsequent microbiological confirmation. Older adults and children may present with atypical symptoms. Children often present with fever and other symptoms such as lethargy, vomiting, and poor feeding.

In this chapter, we summarize the evidence and provide recommendations for the treatment and prevention of uncomplicated lower urinary tract infection in nonpregnant women and in children and men (Table 20.1). We describe the evidence for therapeutic approaches to asymptomatic bacteriuria. Discussions of the treatment of complicated urinary tract infection in all adults and children (including upper tract infection), and uncomplicated urinary tract infection in pregnant women are not included in this chapter.

Epidemiology

Infection of the lower urinary tract accounts for between 1% and 3% of all ambulatory assessments in the United Kingdom and approximately 0.5% of visits in the United States [2, 3]. Urinary tract infection leads to 10–20% of antibiotic prescriptions in ambulatory care [4]. The diagnosis of a urinary tract infection is suggested by the presence of typical urinary symptoms. Confirmation of uropathogenic bacterial species at >100 colony-forming units/ml in the urine indicates infection when symptoms are present. Leucocyte esterase or nitrite positivity on dipstick is highly sensitive in detecting pyuria but may not accurately rule out infection [5]. If the dipstick is negative in the presence of symptoms, urinary culture is appropriate to evaluate further for the diagnosis. Lower urinary tract infections mostly occur through migration of gut-related bacteria into the bladder via the urethra [6]. *E. coli* is the most likely causative organism, occurring in 70–95% of cases, with *Staphylococcus saprophyticus* occurring in about 5–10% of cases and occasionally *Enterobacteriaceae* spp. such as *Proteus* and *Enterobacteriaceae* [7]. Asymptomatic bacteriuria is considered present when there are no urinary symptoms and $>10^5$ colony-forming units of pathogenic bacterial species are detected in the urine.

Urinary tract infections are more common in boys before the age of 6 months, occur at similar rates for boys and girls at 2 years (8%), occur in 1.7% of girls and boys at 7 years, and in 11% and 4% of girls and boys by 16 years [8]. Women are approximately 30 times more likely to experience lower urinary tract infection than men, with almost half of women experiencing one or more infections during their lifetime [9]. The risk is markedly increased after the onset of sexual

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Table 20.1 Treatment for uncomplicated urinary tract infections.

Treatment	Recommendation	Certainty of evidence	Strength of recommendation
Uncomplicated lower urinary tract infection in women			
Antibiotics	We suggest that lower urinary tract infection is treated with nitrofurantoin or trimethoprim/sulfamethoxazole as first-line therapy. Other drug classes may have similar effects (beta-lactams), although resistance may be higher. Fluoroquinolones have no advantage over other antibiotic groups and may increase resistance. We suggest that 3 days of antibiotic therapy is similar to 5–10 days for achieving symptomatic cure for uncomplicated urinary tract infection while longer treatment can be used for bacterial cure in patients for whom this is important.	*High* (symptomatic relief); *moderate* (bacterial cure)	Strong
Recurrent lower urinary tract infection in women			
Antibiotics	We suggest that continuous antibiotic prophylaxis (trimethoprim/sulfamethoxazole, nitrofurantoin, cephalosporin) be used to prevent lower urinary tract infection although the effect is limited to the active antibiotic intake period, the optimal duration is uncertain, and side effects are common.	*Low* (recurrent urinary tract infections)	Weak
Cranberries	We do not suggest cranberries be used to prevent urinary tract infections.	*High* (recurrent urinary tract infections)	Strong
Probiotics	We do not suggest probiotics be used to prevent urinary tract infections.	*Low* (recurrent urinary tract infections)	Weak
Lower urinary tract infection in children and adolescents			
Antibiotics	We suggest children older than 3 months with lower urinary tract infection be treated with trimethoprim/sulfamethoxazole, trimethoprim, or nitrofurantoin as first line. We suggest that 3 days of antibiotic therapy is similar to 5–10 days for achieving symptomatic cure for uncomplicated urinary tract infection while longer treatment can be used for bacterial cure in patients for whom this is important.	*Low* (symptomatic relief, bacterial cure)	Weak
Prevention	We do not suggest long-term antibiotics be used in children with one or more previous urinary tract infections, except in young infants or children with renal abnormalities. We do not suggest that cranberries or probiotics be used to prevent recurrent infection.	*Moderate* (recurrent urinary tract infection, antibiotic resistance)	Moderate
Uncomplicated lower urinary tract infection in men			
Antibiotics	We suggest that lower urinary tract infection in men is treated with nitrofurantoin as first-line therapy. Other drug classes may have similar effects (trimethoprim/sulfamethoxazole, beta-lactams).	*Very low* (symptom and bacterial cure)	Weak
Asymptomatic bacteriuria			
Antibiotics	We do not suggest that antibiotics be used to treat asymptomatic bacteriuria. Screening for asymptomatic bacteriuria in nonpregnant adults and in children is not recommended.	*Moderate* (development of urinary tract infection, side effects)	Moderate

GRADE assessment of the certainty of the evidence [1]: High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different* is low. Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different* is moderate. Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different* is high. Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different* is very high. **Substantially different = a large enough difference that it might affect decision-making*.

activity. Recurrent urinary tract infections are those that occur after appropriate treatment of a previous infection and are usually due to reinfection rather than relapse. One-quarter of women experience a further infection within 6 months of a sentinal urinary tract infection [10].

Pathophysiology

Urinary tract infection occurs due to the migration of uropathic bowel-related organisms (predominantly *E. coli*) that colonize the periurethral opening and which subsequently

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ascend to the bladder [6]. The bacteria then bind directly to epithelial cells (facet cells) in the bladder wall, which then may internalize the adherent organisms [11]. Uropathogenic bacteria may neutralize intracellular lysosomes and enter the bladder epithelial cell cytoplasm. Subsequently, bacteria form clonal intracellular bacterial communities within facet cells and evade innate immune responses when encased within a biofilm [12]. Protein secretion and induction of host gene expression can alter the immune response to bladder wall bacterial invasion and replication. *E. coli* or other bacteria may develop resistance to neutrophil action through morphological changes and reinvade surrounding and previously unexposed bladder wall epithelial cells.

Prognosis

Adult Urinary Tract Infection

Uncomplicated urinary tract infection is associated with a good prognosis in the long term. Among women with an infection sensitive to antibiotics, severe symptoms are expected to last for approximately 3 days, although they may continue for an additional 1.5 days in women with an antimicrobial-resistant organism and somewhat longer overall if antibiotics are not prescribed [13]. Patients may wait almost 5 days before seeking a medical consultation for symptoms which have a moderate impact on activities of daily life, with minimal ongoing impact on usual activities at 10 days [14]. Recurrence of urinary traction infection is most commonly reinfection with the same organism. Following a first urinary tract infection, approximately 25% of women will have a culture-confirmed recurrence within 6 months and 2.7% may have a second recurrence within that time frame [15, 16]. Asymptomatic urinary tract infection is associated with increased risk of urinary tract infection with symptoms, although antimicrobial therapy does not reduce this risk [17].

Pediatric Urinary Tract Infection

In a systematic review, it was reported that between 3% and 15% of children have demonstrable renal parenchymal changes at 1–2 years after a first urinary tract infection [18]. However, it is likely that most children have no cortical renal defects (>80%) and are unlikely to develop new renal damage despite recurrent infection, while the remainder have focal structural abnormalities that may represent congenital or acquired injury [18, 19].

Treatment

Several Cochrane systematic reviews of interventions for treatment and prevention of uncomplicated urinary tract infection have been published. These reviews focus on antibiotic therapy and some nonantibiotic interventions, including cranberries and probiotics as prophylaxis. Most studies of urinary tract infection treatment have used symptomatic cure, bacteriological cure (short-term and long-term), isolation of resistant pathogens, time to symptom resolution, days of work loss, and adverse events, particularly rash and gastrointestinal effects, as critical outcomes. Evidence is most available for nonpregnant women, with a small number of trials involving children, and a paucity of data for outcomes in men with urinary tract infection. Some men (<10%) have been included in trials of women with infection. Trials have evaluated duration of antibiotic therapy, route of administration including oral versus intravenous, and the long-term use of antibiotics to prevent urinary tract infection. There is a limited evidentiary base for evaluation of nonpharmacological interventions.

Treatment of Urinary Tract Infection

Recommendations for Adults

Adult patients with uncomplicated urinary tract infection should receive oral nitrofurantoin or trimethoprim/sulfamethoxazole for 3 days (strong recommendation, high level of evidence). Antibiotic therapy may be reasonably delayed by 48 hours in adults without an indication for immediate treatment (moderate recommendation; moderate level of evidence). Beta-lactam therapy is likely to be equivalent to other first-line antibiotic classes, although local organism resistance may lead to a lower preference of this treatment option. Fluoroquinolones are effective but associated with higher risks of antibiotic resistance. A longer duration of antibiotic treatment (5–10 days) is recommended for women for whom bacteriological eradication might be important (planning pregnancy, recurrent, and painful lower urinary tract infections) and for all men.

Recommendations for Children

Children with uncomplicated urinary tract infection should receive oral antibiotics for 3 days (weak recommendation, low level of evidence). Appropriate antibiotic choices include trimethoprim/sulfamethoxazole, trimethoprim, nitrofurantoin, amoxycillin/clavulanate, or a cephalosporin. Short treatment courses (3 days) have been shown to be as effective as longer duration of therapy (5–10 days).

Evidence in Adults

The different antimicrobial treatments for acute uncomplicated lower urinary tract infection have been evaluated in 21 randomized controlled trials involving over 6000

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participants [20]. Trimethoprim-sulfamethoxazole is as effective as fluoroquinolones, beta-lactam drugs, and nitrofurantoin based on short-term and long-term resolution of symptoms. Rash is more commonly experienced with trimethoprim/sulfamethoxazole compared to nitrofurantoin and fluoroquinolones. Due to higher resistance to beta-lactams in some areas, first-line therapy decisions might include consideration of the potential for adverse events, local microbial patterns, and patient preferences. In a single randomized trial in 300 nonpregnant women, five different management approaches (empirical antibiotics, delayed antibiotics [48 hours], targeted antibiotics based on a symptom score, a dipstick result, or a positive result on a mid-stream urine analysis) achieved similar symptom control. Antibiotic therapy based on dipstick results or delayed prescribing may reduce antibiotic use [21]. In evidence from 32 trials (9605 participants), there was no difference between 3-day and a 5–10-day antibiotic regimen, although the bacteriological failure rate may be higher with 3-day therapy [22]. Adverse events were not surprisingly more common in the 5–10-day treatment groups. Evidence in men is largely derived from trials involving men as a small proportion of the study population and is very uncertain.

Evidence in Children

Sixteen randomized controlled trials involving 1116 children were included in a Cochrane systematic review of antibiotics for treatment children with lower urinary tract infection [23]. The methodological quality of most studies resulted in high or unclear risk of bias for many aspects of trial conduct. This resulted in lower certainty in the evidence and a weak recommendation. A lack of data reduced confidence in understanding whether different classes of antibiotics have different effects, based on outcomes such as persistent bacteriuria, recurrence, or reinfection. There was no evidence that a longer course of treatment (10 days) had different effects than a single dose, except for a higher rate of initial bacterial eradication. Children and young people in the included studies were aged between 2 weeks and 19 years.

Prevention of Urinary Tract Infection

Recommendations for Adults

We suggest in women with two or more documented urinary tract infections in the previous 12 months that continuous antibiotic prophylaxis (trimethoprim/sulfamethoxazole, nitrofurantoin, cephalosporin) might be used to prevent lower urinary tract infection although the effect is limited to the active antibiotic intake period, the optimal duration of treatment is uncertain, and side effects are common (weak recommendation, low certainty evidence). Adults do not benefit from cranberries or probiotics to prevent urinary tract infections.

Recommendations for Children

Children do require antibiotic treatment to prevention urinary tract infection (moderate recommendation, moderate certainty evidence).

Evidence in Adults

In 10 trials involving 430 women, microbiological and clinical recurrence were reduced during the active prophylaxis phase of therapy for 6–12 months duration. In general, the methodological quality of the contributing trials was poor, reducing certainty in the results. In two studies, there was no detectable difference between prophylactic antibiotic use and placebo after completion of antibiotic therapy [24]. In older women with recurrent urinary tract infection, three small trials compared antibiotics with vaginal estrogen therapy, probiotics, or D-mannose powder, antibiotic therapy similarly reduced microbiologically confirmed urinary tract infection episodes during treatment, but there was no apparent effect at 3 months after treatment cessation, although microbiological resistance may have been increased [25].

Cranberries release proanthocyanidins that prevent *E. coli* adherence to bladder wall epithelia [26]. In a Cochrane review published in 2008, it appeared that cranberries might decrease symptomatic urinary tract infections in women, and especially those with recurrent infections [27]. In an updated review that included 24 studies (4473 participants), cranberries did not prevent symptomatic urinary tract infection in women with recurrent infection, older women, children, pregnant women, or those with urinary tract abnormalities [28]. Participants experienced a high drop-out rate, indicating that cranberry juice may not be acceptable over the longer term. In nine studies (735 participants) at high risk of bias involving women and girls with recurrent urinary tract infection, there was no evidence that probiotics prevented symptomatic urinary tract infection [29].

Evidence in Children

A Cochrane review published in 2019 included 16 studies involving 2036 children at often high risk of methodological bias [30]. When analysis was limited to higher quality studies, there was evidence that antibiotics led to a modest reduction in symptomatic recurrence in children with and without vesico-ureteric reflux. Prophylactic antibiotics possibly increased microbiological resistance. There was no evidence in two Cochrane reviews that cranberries or probiotics prevented urinary tract infection in children [28, 29].

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Treatment of Asymptomatic Bacteriuria

Nonpregnant adults and children with asymptomatic bacteriuria and a normal or noninstrumented urinary tract do not require antibiotic therapy. Nonpregnant adults do not benefit from screening for asymptomatic bacteriuria.

Evidence in Adults

In a Cochrane view that included nine studies and 1614 participants, antibiotic therapy of asymptomatic bacteriuria had no detectable effect on symptomatic urinary tract infection or complications [31]. Studies were generally of high or moderate methodological quality. Antibiotics increase the likelihood of bacteriological cure, at the expense of increased adverse events. Limited data were available for understanding the impact of antibiotic therapy on microbial resistance. In data from a randomized controlled trial and a prospective cohort study, there was no evidence that screening for asymptomatic bacteriuria is effective [32].

Evidence in Children

There is insufficient evidence to be certain whether antibiotic therapy benefits children in the long term. The impact on kidney injury or harmful effects of providing treatment are uncertain [33].

Patient Perspectives

In qualitative analysis, women with symptomatic urinary tract infection preferred to avoid antibiotic therapy and would consider nonantibiotic-based approaches. Prior experiences of antibiotics led to a greater acceptance of this approach, while a "delayed antibiotic" strategy was preferred by most women but was viewed as lack of validation for symptoms and being taken seriously by some [34].

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21a

Toxic Nephropathies: Environmental Agents and Metals

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Introduction

Environmental nephrotoxins include materials found predominantly in the workplace [1–3] (Table 21a.1). Many of these chemicals have no biological value for the treatment of diseases and are toxic to many tissues and cells. The clinically important industrial nephrotoxins include lead, mercury, cadmium, silica, a variety of (sometimes poorly defined) organic hydrocarbons (aliphatic, aromatic, and halogenated), uranium, chromium, and arsenic [4]. Most of these nephrotoxins cause biological exposure through inhalation and ingestion of contaminated food and drinks. Although low concentrations of heavy metals are present in the environment naturally, there is a greater exposure to these nephrotoxins in industrial and developed countries. For many of these nephrotoxins [5], it should be recognized that there are no randomized controlled trials for the management of kidney diseases caused by these environmental agents. The cornerstone of treatment is prevention and limiting further exposure (Table 21a.2).

Heavy Metals

Lead

Acute lead poisoning continues to rise in most developed countries and in particular in socio-economically deprived communities [6]. Acute lead poisoning causing abdominal pain, anemia, and encephalopathy may occur days or weeks after exposure to lead. Blood lead levels exceeding 70 μg/dl (current mean blood lead in the USA is <2 μg/dl) are associated with acute lead toxicity [7]. Acute childhood lead poisoning usually occurred because of the ingestion of lead-based paint in deteriorated housing. Fanconi syndrome (aminoaciduria and phosphaturia) has been reported in children with acute lead toxicity. This finding is consistent with transient proximal tubular reabsorptive defects [8]. Fanconi syndrome is regularly reproducible in experimental animals exposed to sufficiently high doses of lead. Lead-induced Fanconi syndrome is reversible with chelating therapy ($CaNa_2$–EDTA) and removal from exposure [9].

In acute lead toxicity states, there is a clear relationship between plasma level and toxic exposure. The diagnosis and treatment are much more difficult in the long-term, low-dose exposure of lead in adults. In addition, many comorbid conditions might mask the signs and symptoms of chronic lead toxicity [5, 10]. Chronic lead exposure is also associated with hypertension, gout, and tubulointerstitial nephritis, which is histologically indistinguishable from hypertensive nephrosclerosis. In the past, lead nephropathy was identified in lead workers or those working with moonshiner (illegal use of distilled liquor) after chronic exposure [2]. Blood lead in these workers was often above 40 μg/dl, which is the exposure limit promulgated in the federal occupational lead standard. It was widely assumed that blood lead levels of 60 μg/dl or higher, sustained for many years, were required to induce lead nephropathy. However, recent epidemiologic evidence using blood and bone lead measurements (by noninvasive in vivo K X-ray fluorescence) indicate that the adverse effects of lead on blood pressure and kidney function occur at much lower levels than previously recognized. Ninety-five percent of lead in the body is retained in bone, with a biological half-life approximating two decades, whereas

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Table 21a.1 Environmental nephrotoxins.

	Pathology			
Substance	**ATN**	**TIN**	**G**	**Comments**
Metals				
Pb	+	+	−	Fanconi syndrome, tubular proteinuria, hypertension, gout
Cd	−	+	−	Fanconi syndrome, Ca^{++} wasting, tubular proteinuria
Hg[a]	+	+	+	G → immune, genetic control, nephrotic syndrome; $HgCl_2$ → ATN
As	+	+	−	AsH_3, hemolysis
Cr[a]	+	+	−	Cr^{+++} → tubular proteinuria, nasal perforation, cancer; Cr^{+++++} → ATN
U	+	+	−	Tubular proteinuria
Si	−	−	+	Immune adjuvant, immune complexes, ANCA, Wegener's granulomatosis
Organics				
CCl_4	+	+	−	Liver damage, alcohol enhanced, dry cleaner
Toluene	−	−	−	Tubular proteinuria, glue sniffing
Solvents	−	−	+	Immune G, tubular proteinuria
Selected drugs[b]				
Aminoglycosides	+	+	−	ARF after 8 days, lysosomal accumulation S_1 and S_2
Amphotericin B	−	+	−	Distal RTA, K^+↓, Mg^{++}↓, Uosm ↓, tubular calcification
Penicillins	−	+	−	Allergic component, acute, after 15 days, interstitial edema, lymphocytic infiltration
Vancomycin	+	+	−	ARF
Sulfonamides	−	+	−	Intra-luminal crystals, kidney stones, ARF, microhematuria, soluble in alkaline urine
Acyclovir	−	+	−	Intraluminal crystal deposition, flank pain, microhematuria
Cyclosporin A Tacrolimus	+	+	−	ARF, vasomotor, proximal tubule vacuolization, striped fibrosis, arteriolar hyalinosis
Gold salts	−	+	+	Membranous glomerulopthy, gold in tubular epithelium, separate tubular disease
D-penicillamine	−	−	−	Membranous glomerulopthy, vasculitis
cis-platinum	+	+	−	ARF, usually reversible
Mitomycin	−	+	−	Thrombosis, hemolytic uremic syndrome

ANCA, anti-neutrophil cytoplasmic antibody; ARF, acute renal failure; ATN, acute tubular necrosis; G, glomerulopathy; RTA, renal tubular acidosis; TIN, tubular interstitial nephritis; Uosm, urine osmolality.
[a] Depends on valance and organic form.
[b] Often in clinically complex settings with multicausal renal damage.

blood lead has a biological half-life of about 30 days [11]. Therefore, bone lead reflects cumulative lead absorption, whereas blood lead primarily reflects recent exposure.

Blood lead and bone lead predict blood pressure even when both are within the range traditionally considered "normal." Epidemiologic evidence that low-level lead absorption (blood lead of <10 μg/dl) has deleterious effects on blood pressure and renal function was obtained from National Health and Nutrition Evaluation Survey III, 1988–1994. Analysis of data on over 15 000 Americans showed that hypertensive people had significantly higher blood lead levels (4.21 vs. 3.30 μg/dl) than people without hypertension [11, 12]. Two large, cross-sectional studies also reported a significant association between low-level lead exposure and serum creatinine [7, 12]. The adverse effects of low-level lead exposure on renal function are further supported by longitudinal observations. Because lead does not accumulate in patients with kidney failure of non-lead etiology, these observations point to low-level lead exposure as a contributor to hypertension and kidney disease.

Bone lead levels were found to be significant predictors of hypertension in community-exposed men [13]. The mean blood lead level in these men was 6 μg/dl. Similarly, bone lead levels were found to be a significant predictor of hypertension in nurses [14]. A study in pregnant women

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Table 21a.2 Treatment of environmental exposures.

Metals	Treatment
Pb	$CaNa_2$–EDTA, dimercaprol, succimer, or penicillamine
Cd	EDTA and supportive measure
Hg[1]	Dimercaprol, succimer
As	Dimercaprol, succimer
Cr[1]	Supportive measures and avodiance
U	Supportive measures and avodiance
Si	Supportive measures and avodiance
Organics	
CCl_4	Supportive measures and avodiance
Toluene	Supportive measures and avodiance
Solvents	Supportive measures and avodiance

$CaNa_2$–EDTA, calcium ethylenediaminetetraacetic acid.

with a geometric mean blood lead level of 1.9 μg/dl found increases in bone lead were associated with an increased risk of pregnancy hypertension [15]. Increases in both diastolic and systolic blood pressures in pregnant women were significantly associated with blood lead, and the major portion of the effect was found with blood lead levels under 5 μg/dl. These observations on adverse effects at blood lead levels below 10 μg/dl in diverse groups indicate that, even at levels traditionally considered acceptable, important adverse health effects occur.

Treatment of lead-induced hypertension and kidney failure with calcium ethylenediaminetetraacetic acid ($CaNa_2$–EDTA; also called calcium disodium versenate or edetate calcium disodium) may improve the glomerular filtration rate (GFR) or reduce the rate of progression of kidney failure. However, there is no clinical data to support the reversibility of established interstitial nephritis after treatment with $CaNa_2$–EDTA [16, 17]. It is reasonable to do an EDTA lead mobilization study and 24-hour urine collection in patients with unknown causes of hypertension, gout, and potential exposure to lead. Therapeutic benefits have been noted in patients with acute kidney injury from much lower levels of lead exposure. Lin et al. [11] treated patients with chronic kidney disease (CKD) from lead exposure (mean creatinine 2.1 mg/dl, mean blood lead 5.3 μg/dl) with $CaNa_2$–EDTA, 4–13 g intravenously, over 2 years. The treated group had a modest improvement in GFR averaging 3.4 ml/min, whereas untreated controls had a decrease in GFR of 1.0 ml/min during this period. The same laboratory demonstrated that low levels of lead absorption correlate significantly with the rate of progression of kidney failure in type 2 diabetics and that $CaNa_2$–EDTA therapy, averaging 7 g over 3 months, significantly reduced the rate of progression of kidney failure compared to untreated diabetic controls. These results suggest that reducing even very low levels of lead may improve GFR in a variety of nonlead-related kidney diseases. Moreover, if the beneficial effect of $CaNa_2$–EDTA is, in fact, due to the removal of lead from the body, these observations indicate that there is no threshold for the deleterious effects of lead on kidneys [18].

However, the mechanism of the beneficial effect of $CaNa_2$–EDTA on the kidneys is not clear. Improvement and management of comorbid conditions may play an important role in the improvement of hypertension and reduced GFR. Prevention remains the most effective method of treatment of lead poisoning. Chelation transiently increases the rate of removal of lead, causing the urinary excretion of up to several milligrams of lead in heavily exposed individuals within a few days. If, on the other hand, excessive exposure is terminated, the expected urinary excretion of 100–200 μg of lead/day will achieve a negative balance of 35–70 mg/year. Because a lifetime of occupational exposure can result in bone lead stores of 500 mg or more, a course of chelation therapy (e.g. 1–2 g $CaNa_2$–EDTA) eliminates only about 0.2–0.4% of the body burden, whereas terminating exposure reduces bone stores by about 10% per year. Although it is not feasible to eliminate all lead intake, similar calculations for individuals with low-level exposure indicate that, in the long term, prevention is more effective than chelation in lowering the body lead stores. In summary, chelation therapy is justified in cases of symptomatic lead poisoning or when the blood lead exceeds about 70 μg/dl, but when no symptom end point is clearly defined, chelation for blood lead of <70 μg/dl is not usually justified [8].

Mercury

Exposure to mercury can be through inhalation, oral, or dermal. Mercury is a natural element with atomic weight of 200.6. There are many form of organic and inorganic mercury in the pharmaceutical industry. Mercury is unique in that it exists as a liquid at room temperature. Inorganic mercury mostly accumulates in the kidney while organic mercury mostly accumulates in the central nervous system. A number of studies have suggested that patients/animals with reduced renal function are at greater risk of mercury renal toxicity [19]. The salt of mercury thimerosal is still used in vaccines as a preservative. The toxicity of mercury depends on both its chemical form and the route of absorption. Although preferentially accumulated in the kidney, neurologic disease, but not kidney disease, regularly follows exposure to elemental mercury. Once in the

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environment, elemental mercury undergoes biotransformation to both organic and inorganic salts, which are absorbed by living organisms and thus enter the food chain. Mercury at the cellular level accumulates at proximal tubular cells via OAT-1 and 3. Mercury may alter the function and structure of nephrons. After exposure to a toxic dose of mercury exposure, mitochondrial swelling and dilation of the endoplasmic reticulum of proximal tubular cell can be identified [20].

In addition to diuresis and acute tubular necrosis, mercury has been sporadically reported to cause nephrotic syndrome in what has usually been considered an idiosyncratic response. Observations in rats may provide a framework for understanding mercury-induced glomerular disease in humans. In 1971, Bariety et al. [21] reported that multiple subcutaneous injections of $HgCl_2$ in specific rat strains, in doses too small to produce tubular necrosis, induced membranous nephropathy. Kidney disease characterized by glomerular deposition of immune complexes and heavy proteinuria developed in about 2 months. Subsequent studies showed that the immune response is actually biphasic; immune complex deposition is preceded by antiglomerular basement membrane antibody and complement deposition. The response to mercury in the rat is under precise genetic control. As little as 0.05 mg/kg of body weight will elicit immunologically mediated glomerular disease in selected strains. As in humans, mercury-induced glomerular disease in rats is self-limited [22].

There are no randomized clinical trials for the treatment of acute tubular necrosis or nephrotic syndrome due to mercury. Chelation therapy has been employed for excessive mercury exposure, often defined as more than 5 μg Hg/dl in blood or 50 μg Hg/l in urine, but evidence for the effectiveness of chelation therapy is lacking. Traditional use of BAL (British antilewisite, dimercaprol) for chelating mercury is currently being replaced by its soluble congeners, dimercaptopropane sulfonic acid (unithiol or Dimaval) and succimer (dimercaptosuccinic acid, Chemet). Dimercaptopropane sulfonic acid is the chelator of choice for inorganic mercury intoxication, whereas succimer is the agent of choice for organic mercury [22]. Case reports suggest that in the presence of severe kidney failure the mercury-chelate complex can be removed by hemodialysis or hemofiltration.

Cadmium

Cadmium (Cd) is an environmentally prevalent heavy metal and pollutant that is known to have multiple adverse effects on the human body and is most commonly found in batteries, plastics, pigments, and fertilizers [23]. Given its role in fertilizers, Cd can accumulate in both plants and animals. As a result, diet becomes the primary route of exposure among the nonsmoking population [24]. However, in the smoking population, inhalation is the primary route of exposure as tobacco plants accumulate Cd in high concentrations. Verdugo et al. investigated the concentration of Cd in cigarettes and found that 1–2 μg of Cd were present in each cigarette, of which 5% is absorbed by the lungs [25–27].

Once Cd is absorbed systemically, it accumulates in multiple organs, including bone and liver, like other heavy metals, but also in the kidney. As much as 50% of the total body stores are found in the kidney, which explains the significant renal adverse effects associated with Cd [28, 29]. Cadmium deposition in the bone results in a long half-life, requiring decades for complete elimination. Complete elimination, however, is difficult because of the chronic low-dose exposure that may initially go unnoticed until large burdens accumulate.

While renal handling of Cd is complex and not fully understood, it is known that Cd has a high affinity for sulfhydrl moieties, and is suspected to be transported along with organic anions/cations and amino acids or oligopepties [30]. Additionally Cd utilizes other metal transports such as divalent metal transporter (DMT1) and zinc transporters such as ZIP8 and ZIP14 to cross cell membranes. Despite these routes, it is suspected that most Cd enters the proximal tubular epithelial cells after being transformed to Cd-metallothionein [MT] by the liver. Cd-MT is a nontoxic byproduct that usually accumulates in the liver, but may be released through Cd-induced hepatocellular necrosis, resulting in serum Cd-MT, which is subsequently absorbed by the proximal tubular epithelium via endocytosis [30, 31]. Once in the kidney, Cd disassociates from MT in the lysosomes where it may lead to renal adverse effects. Accumulation of Cd in the kidney typically causes polyuria, reduced GFR, and Fanconi syndrome [28].

Thought rarely tested, cadmium monitoring can be done through urine and or blood assays. Serum levels are helpful for acute exposures (within the last month), whereas urinary sampling is utilized when chronic exposure is suspected. Given that most people are exposed chronically at low dose, urinary excretion of Cd is a more reliable indicator, especially when it comes to renal and total body burden [23, 32]. Monitoring for kidney damage typically involves nonspecific signs including urinary biomarkers, β2-microglobulin, *N*-acetyl-β-D-glucosamidase (NAG), kidney injury moleculre-1 (KIM-1), and cystatin C [28], the latter being a more reliable biomarker for Cd-induced damage [33]. Prolonged Cd exposure typically manifests as proximal tubular microvilli damage, resulting in reduced transporters and reabsorption. If severe enough, Fanconi syndrome may be diagnosed, which is characterized by aminoaciduria, glucosuria, hypercalciuria, and hyperphosphaturia. While kidney damage has

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multiple negative downstream effects, nonrenal adverse events occur such as decreased synthesis of activated vitamin D (1,25-dihydroxycholecalciferol) and liver damage.

Multiple epidemiological studies have documented a dose-related correlation to renal insufficiency, but given the high incidence and prevalence of CKD in the world, one must have a high clinical suspicion to diagnose Cd-induced CKD. This most typically occurs in places with high incidence of Cd in the environment such as Sri Lanka [34]. As CKD develops and GFR declines, there is a reduced capacity to clear the nephrotoxin, exacerbating preexisting renal disease [35–38].

Excretion occurs very slowly given the distribution and deposition in the bone, but risk factors such as age, gender, and diabetes decrease excretion. One study reported decreased urinary Cd was associated with diabetic rats compared to nondiabetic rats [4]. Although not fully understood, some studies have shown decreased insulin expression in Cd exposure, but this is confounded because both Cd and diabetes cause renal disease, which has been shown to decrease excretion. Interestingly, studies assessing the differential burdens of Cd between men and women found women to have greater burdens compared to men. Further investigation revealed that both blood and urinary Cd levels correlate with age and iron stores. On average women tend to have lower iron stores than men and as a result of the lower iron stores, they upregulate DMT1 in an attempt to absorb more iron. This also facilitates Cd uptake through the same transporter, ultimately predisposing those with low iron to increased Cd uptake [39–41].

Once cadmium has been detected in the body at toxic levels, treatment is primarily through chelation therapy with succimer or EDTA. Further research still has to be done, but other metals such as zinc and magnesium have been shown to limit renal toxicity. While the mechanism of action is likely multifactorial, it has been shown to prevent enzyme alteration as well as saturate metal transporters. This hinders the further uptake of Cd into both the cell and the body. While no agents are particularly effective for removing Cd from the liver, zinc has been shown to help transform Cd to the nontoxic form (Cd-MT) and reduce cellular apoptosis induced by Cd [42–44]. Overall, to diagnose Cd toxicity, one must have a high suspicion for it as exposure is commonly low dose and chronic. Despite limited interventions, diagnosing cadmium toxicity enables environmental assessment in an attempt to reduce exposure and limit further damage.

Itai-Itai Disease

In Japan, a painful bone disease associated with pseudofractures due to cadmium-induced renal calcium wasting was recognized in the 1950s. Attributed to local contamination of food staples by river water polluted with industrial effluents, the syndrome, known as itai-itai or "ouch-ouch" disease, primarily afflicted postmenopausal, multiparous women. Sustained deficiencies in iron, zinc, calcium, and vitamin D rendered these women particularly vulnerable to cadmium toxicity [45]. Women with itai-itai disease tended to have reduced GFR, anemia, lymphopenia, and hypotension as well as osteomalacia. They exhibited a waddling gait, short stature, anemia, glycosuria, and elevated serum alkaline phosphatase levels. Hypertension was absent. β2-microglobulin excretion exceeded the normal maximum (1 mg/g of creatinine) by 100-fold, and GFR was substantially reduced in the most severely affected individuals. Long-term follow-up studies showed that excessive urinary excretion of the low-molecular-weight protein β2-microglobulin predicts the later development of kidney failure in patients with itai-itai disease and that kidney damage progresses even after exposure has ceased. Succimer is effective for chelation in acute cadmium poisoning [22]. No agent has been found to be effective for mobilizing hepatic or renal stores of cadmium [2, 46].

Silicon

Silicon is a semimetal found as the dioxide (SiO_2, silicon dioxide) in 28% of the earth's crust. It has been reported to induce interstitial nephritis by direct deposition of crystalline material in the renal parenchyma [47] and by immunologic mechanisms acting as an adjuvant to stimulate the immune response [48]. Tubular proteinuria is found in workers exposed to silica dust. The odds of a sandblaster developing end-stage renal disease is 3.8 compared to matched controls. In the accelerated form of silicosis known as silicoproteinosis, silicon dust appears to be indirectly responsible for rapidly progressive, immune complex-mediated focal glomerulosclerosis [49]. In addition to severe pulmonary disease, these patients develop an overwhelming autoimmune response that frequently includes lupus erythematosus [23] or rheumatoid arthritis (Caplan's syndrome). Glomerular disease, sometimes in association with silica-induced systemic sclerosis, systemic lupus erythematosus, and small vessel vasculitis, has also been described as a result of exposure to silica dust independent of silicosis [24]. Antineutrophil cytoplasmic antibody (c-ANCA)-positive Wegener's granulomatosis has been associated with exposure to silica dust as well as to silica-containing compounds, such as grain dust. No specific therapies have been reported for silica-induced glomerular disease other than those in current use for immunologically medicated glomerular disease [3].

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Solvent Nephropathy

Halogenated hydrocarbons have often been implicated in the induction of acute tubular necrosis or Fanconi syndrome in both humans and experimental animals. Low-level occupational absorption by inhalation of volatile hydrocarbons or absorption through the skin may also induce tubular proteinuria, which does not necessarily signify the presence of clinical kidney failure.

At least 40 case-control studies have examined the relationship between glomerulonephritis and exposure to organic solvents. A number of these studies concluded that patients with chronic glomerulonephritis had been exposed to organic solvents (aliphatic and aromatic) more frequently than patients with other diseases. Initially, solvent nephropathy was associated with antiglomerular basement membrane antibody-mediated glomerulonephritis and pulmonary hemorrhage, i.e. Goodpasture's syndrome, but later reports of solvent nephropathy have included many different types of glomerulonephritis [50].

The etiologic role of solvents remains controversial because the dose and exact chemical composition of industrial solvents are usually unknown. Moreover, of the thousands of workers exposed, very few develop immunologically mediated glomerular disease. The genetic and environmental factors that make specific individuals susceptible to solvent nephropathy have not been delineated. The experimental mercury-induced immunologically mediated glomerular disease in rodents described above may provide a model for understanding solvent nephropathy in humans. No specific therapies have been recommended for solvent nephropathy. Avoidance of exposure to volatile hydrocarbons and their derivatives remains an essential preventive approach.

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21b

Toxic Nephropathies: Nonsteroidal Anti-inflammatory Drugs

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Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are one of the most commonly prescribed groups of drugs for the treatment of pain and inflammation. It is estimated that, worldwide, more than 30 million people take NSAIDs daily [1]. The precise incidence of renal disease related to NSAIDs is difficult to estimate due to the heterogeneity of the population. In general, approximately 1–3% of the patients taking NSAIDS may manifest one or more kind of renal injury from acute or chronic use of NSAIDS [2]. Thus, the widespread use of NSAIDs means that renal complications are observed relatively frequently in clinical practice. Complications include hypertension, edema, salt and water retention, acute tubular necrosis, acute interstitial nephritis, hyperkalemia, as well as acute and chronic kidney failure [3]. In addition, NSAIDs may worsen preexisting hypertension, heart failure, and electrolyte imbalance and cause acceleration and progression of kidney disease [4, 5].

In addition to renal side effects, NSAIDs also have significant gastrointestinal complications such as ulcers and bleeding. Furthermore, the use of NSAIDS at higher doses is associated with increased risk of cardiac events, such as myocardial infarctions, acute coronary syndromes, and strokes.

Two different iso-enzymes of cyclooxygenase (1 and 2) have been identified. Both enzymes play an important role in platelet aggregation, gastrointestinal integrity, and cardiovascular health [6]. It has been hypothesized that nonselective NSAIDs inhibit both constitutive cyclooxygenase 1 (COX-1) and inducible COX-2, the rate-limiting enzymes that are involved in the production of prostaglandins and thromboxane A2, while selective COX-2 inhibitors only inhibit inducible COX-2. Originally, three COX-2-selective NSAIDs, namely celecoxib, rofecoxib, and valdecoxib, were approved. They were designed with the hope of exhibiting anti-inflammatory properties while lacking the deleterious effects on homeostatic functions mediated by COX-1 activation such as gastrointestinal ulcers and bleeding; however, increased myocardial infarctions and ischemic strokes were reported with all agents when used at higher than recommended dosage compared to placebo or other NSAIDs [7]. In the Vigor study, a 79% greater risk of death or serious cardiovascular events was found in one treatment group compared with the other, rofecoxib ($P = 0.007$) [8], and increased cardiovascular events in patients who underwent coronary artery bypass surgery and received valdecoxib [9]. This led to their withdrawal from the market in 2004 and 2005, respectively. Recently, the results of the PRECISION study were published [10]. Among patients requiring a moderate dose of daily NSAID treatment, the incidence of cardiovascular disease, cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke for celecoxib [200 mg daily] was noninferior to ibuprofen and naproxen. However, the incidence of renal events was significantly lower with celecoxib versus ibuprofen.

Low-dose aspirin irreversibly inhibits platelet COX-1, thereby blocking the synthesis of thromboxane A_2, a prothrombotic factor, and has little effect on endothelial COX-2 derived prostacyclin [11]. Prostacyclin inhibits platelet aggregation and leads to vasodilatation. Due to its selectivity, low-dose aspirin is the drug of choice for the prevention of thrombotic events, even in patients with

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underlying kidney disease, without the risk of jeopardizing prostaglandin-dependent kidney function. By contrast, higher doses of aspirin can inhibit COX-2-derived prostacyclin production. Prostacyclin is mainly COX-2 derived and is inhibited by both nonselective NSAIDs and COX-2-selective NSAIDs. Therefore, a potential cardiovascular risk is seen with nonselective NSAIDs as well as COX-2-selective drugs [12–14].

Actions of Renal Prostaglandins

Both COX-1 and COX-2 are expressed extensively in the kidney. COX-2 activities have been identified mostly in the macula densa and medulla while COX-1 works in the glomerulus and both cortical and medullary collective ducts [15, 16]. The kidney produces the vasodilator prostaglandins PGE_2, $PGF_2\alpha$, and PGI_2 as well as vasoconstrictive thromboxane A_2. These autocoids, synthesized and metabolized by the kidney, autoregulate renal blood flow, renin release, tubular ion transport, and water metabolism [17, 18]. PGI_2, which is mainly present in the afferent arteriole and glomerulus, plays a major role in controlling glomerular hemodynamics [19]. In contrast, PGE_2, which is predominantly produced in the collecting tubule and within the interstitium, regulates medullary hemodynamics [18].

Effects on COX-2 NSAIDs on Renal Prostaglandins

All NSAIDS, nonselective or selective, prevent prostaglandin synthesis in the kidneys. The urinary excretion of PGE_2 and 6-keto-$PGF1_a$, the stable metabolite of PGI_2, reflects the renal synthesis of PGE_2 and PGI_2, respectively. In healthy older adults, rofecoxib reduces baseline urinary 6-keto-$PGF_1\alpha$ by 47%, comparable to the 53% reduction induced by indomethacin [20]. In another study, rofecoxib reduced urinary PGE_2 and 6-keto-PGF1α excretion in healthy volunteers by approximately 40–50%, similar to that induced by meloxicam or diclofenac [21]. This inhibition has a profound effect on hemodynamic compensatory mechanism in the kidneys.

Furthermore, excretion of urinary 6-keto-$PGF_1\alpha$ was comparable in response to celecoxib and traditional NSAIDs [22]. In a trial of healthy elderly volunteers consuming normal amounts of sodium, multiple doses of twice-daily celecoxib reduced PGE_2 and 6-keto-PGF1α excretion to the same degree as naproxen, by approximately 65 and 80%, respectively [23]. These data suggest that the COX-2 isoform plays an important role in renal prostaglandin biosynthesis. It is thus likely that COX-2 inhibitors will impact renal function just as nonselective NSAIDs do.

Maintenance of Renal Blood Flow and Glomerular Filtration Rate

NSAIDs produce negligible effects on the renal hemodynamics of most young and healthy euvolemic subjects [24, 25]. However, in hemodynamic compromised subjects, NSAIDS are associated with number of renal syndromes. Prostaglandins maintain renal blood flow and glomerular filtration rate despite vasoconstrictor stimuli, such as leukotrienes, thromboxane A_2, angiotensin II, vasopressin, endothelin, and catecholamines. Though vasoconstrictive, catecholamines stimulate local prostaglandin production, resulting in a feedback loop between vasoconstrictors and vasodilatory prostaglandins [26–28]. $PGF_2\alpha$-like peroxidation products also have major vasoconstrictive effects [29]. Thus, in patients with underlying ischemic or inflammatory renal injury, the addition of a nonselective or COX-2-selective NSAID not only decreases the production of vasodilatory prostaglandins but also results in the nonenzymatic formation of vasoconstrictor metabolites of arachidonic acid, further jeopardizing renal blood flow and glomerular filtration. However, in the presence of salt depletion, an ineffective circulating plasma volume, or under conditions characterized by high circulating levels of vasoconstrictor hormones, NSAIDs may be nephrotoxic. Such conditions include cirrhosis, hypovolemia, cardiac disease, renal disease, septic shock, advanced age, diuretic use, diabetes mellitus, and following surgery [30].

In elderly, salt-replete subjects, both indomethacin and rofecoxib decreased sodium excretion, but only indomethacin reduced the glomerular filtration rate [20]. Celecoxib, like rofecoxib, affects renal function in selected groups of subjects. Whelton et al. compared celecoxib with naproxen in 29 healthy elderly subjects in a single-blind, randomized, crossover study [31]. Subjects were given either celecoxib at 200 mg twice daily for 5 days followed by celecoxib at 400 mg twice daily for the next 5 days or they received naproxen at 500 mg twice daily for 10 days. After a 7-day washout, subjects were crossed over to the other regimen. Glomerular filtration rate fell more with naproxen than with celecoxib, although urinary excretion of prostaglandin E_2, 6-keto-PGF1α, and sodium was comparable. In another study involving salt-depleted elderly subjects, rofecoxib and indomethacin induced a comparable reduction of glomerular filtration rate [32]. These studies illustrate that COX-2 inhibitors and nonselective NSAIDs have similar effects on renal hemodynamics.

Postoperative Use of NSAIDs

Lee and coworker in a meta-analysis of 19 trials ($n = 1024$) demonstrated that the postoperative use of NSAIDs in adults with normal preoperative renal function resulted in

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Table 21b.1 Patients at risk for renal impairment.

Heart failure; EF less than 40%
Liver disease
Patients with SCr > 1.5 mg/dl
Elderly population
Dehydration (protracted-several days)
Concomitant use of nephrotoxins (cyclosporine, tacrolimus, aminoglycoside, etc.)

SCr, serum creatinine.

a 16 ml/min fall in creatinine clearance (95% confidence interval [CI] 5–28) and a fall in potassium excretion of 38 mmol/day (95% CI 19–56) on the first day after surgery compared with placebo [33]. No cases of postoperative acute kidney failure requiring dialysis were reported. The conclusions were that NSAIDs caused a clinically unimportant reduction in kidney function in the early postoperative period in patients with normal kidney function and that these drugs should not be withheld in such patients. Others have reported, however, an overall incidence of postoperative renal insufficiency of 18% after major surgery, with a subsequent hospital mortality rate of 13% [34]. In general, NSAIDs should be withheld from patients at risk for kidney injury or patients with preexisting kidney disease pre- and postoperative because of concerns about their effects on renal function [3] (Table 21b.1).

Renal Dysfunction in COX-2 Trials

In one study, renal adverse events were reported in 24.3% of 144 patients receiving celecoxib and in 30.8% of 143 patients receiving diclofenac and omeprazole. Kidney failure (defined as a rise in serum creatinine to above 200 μmol/l) was seen in 5.6 and 6.3% of patients, respectively [35]. Overall, renal adverse events were more common in patients with renal impairment (celecoxib 51.4%, diclofenac plus omeprazole 40.7%). In another study, adverse effects related to kidney function occurred in about 1% of naproxen- and rofecoxib-treated patients [8]. In a review of randomized clinical trials lasting 2 weeks or more involving celecoxib, a rise in serum creatinine was seen in 0.7% of patients treated with celecoxib and in 1.2% of patients treated with diclofenac ($P < 0.05$) [36]. In a meta-analysis of data from company clinical trial reports, there was no difference in the incidence of renal adverse events (defined as an increase in serum creatinine >1.3 times the upper limit of normal) in 15 319 patients treated with celecoxib (0.3%) or other NSAIDs (0.5%) (relative risk [RR] 0.78, 95% CI 0.48–1.3) [37]. In summary, from these trials, there are no differences in renal side effects between COX-2-selective inhibitors and nonselective inhibitors. In the PRESION study, the serum creatinine level of ≥2.0 mg/dl (177 μmol/l), an increase of verified serum creatinine level of ≥0.7 mg/dl (62 μmol/l) from baseline or doubling of the baseline serum creatinine, or hyperkalemia (defined as >6 mmol/dl) with ≥50% elevation in serum creatinine and initiation of hemodialysis or peritoneal dialysis were comparable between naproxen and celecoxib while much higher for ibuprofen (0.5% vs. 0.9% $P = 0.004$) [10]

Renin Release and Potassium Homeostasis

PGE_2, PGI_2, and arachidonic acid are potent stimuli of renin release [15]. Both nonselective and COX-2-selective NSAIDs can inhibit renin secretion and under some circumstances lead to hyporeninemia and hypoaldosteronism with attendant hyperkalemia. This is particularly common in patients with preexisting renal impairment [38–40]. Inhibition of prostaglandin synthesis can also lead to hyperkalemia by decreasing distal tubular flow rate and sodium delivery, both of which limit potassium secretion [41, 42].

Natriuresis and Diuresis

Renal prostaglandins are natriuretic and diuretic. They inhibit sodium and chloride reabsorption in the proximal and distal nephrons as well as in the loop of Henle [43, 44]. In addition, renal prostaglandins reduce the renal corticomedullary solute gradient and antagonize the action of vasopressin in vivo [45]. Although prostaglandins acutely influence salt and water excretion, they do not regulate it under normal conditions.

Clinical Syndromes Associated with Nonselective and COX-2-Selective NSAIDs

Acute Renal Impairment and Acute Tubular Necrosis

Under circumstances where there is poor renal perfusion with high renin levels, nonselective and COX-2-selective NSAIDs can reduce glomerular filtration rate, resulting in acute kidney failure. This complication has been reported with most NSAIDs but only rarely with aspirin. Kidney failure has also been described after administration of topical and intramuscular NSAIDs [46–48].

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A multicenter study in France examined the incidence and subsequent outcome of patients with drug-induced acute kidney failure [49]. Of the 398 patients with acute kidney failure, 147 (36.9%) had taken NSAIDs. One-third of them required dialysis, and 71.4% recovered or regained previous renal function. A renal biopsy obtained in 25 patients with NSAID-associated kidney failure disclosed acute tubular necrosis and acute interstitial nephritis in 21 patients and either minimal change nephropathy or chronic renal damage in four. A nested case–control study using the United Kingdom General Practice Research Database reported that current users had an RR of developing acute kidney failure of 3.2 (95% CI 1.8–5.8) compared with non-NSAID users [50]. This increased risk was higher in patients with heart failure, hypertension, or diabetes. Thus, although renal side effects from NSAID use are relatively rare, renal damage can be irreversible and the outcome can be fatal. Renal function usually improves upon drug withdrawal, although in some cases permanent renal damage may occur [51].

Acute kidney failure and hyperkalemia have been observed after the administration of COX-2-selective inhibitors to patients with risk factors for NSAID-induced acute renal insufficiency, including underlying chronic renal impairment and volume depletion [52]. Acute kidney failure was also reported in a patient with a kidney transplant 4 weeks after starting rofecoxib [53].

Acute Tubulo-Interstitial Nephritis

NSAIDs of different classes have been associated with acute tubulo-interstitial nephritis and kidney failure [2, 51, 54, 55]. Acute allergic tubulo-interstitial nephritis due to NSAIDs is much less common than hemodynamic kidney failure. The patients are often elderly and may have taken the offending agent for months or years before the development of acute interstitial nephritis. Clinical evidence of an allergic reaction, such as fever, rash, arthralgia, eosinophilia, or eosinophiluria, is uncommon. Of note, proteinuria, often in the nephrotic range, may occasionally appear, especially in fenoprofen-induced tubulo-interstitial nephritis [54, 56, 57]. Cases of interstitial nephritis have been reported with both celecoxib and rofecoxib [58–64]. In two cases, interstitial nephritis was associated with glomerulopathies, one case with minimal change disease [62] and the other one with membranous nephropathy [58]. Thus, there is little evidence that suggests a major difference between NSAIDs and COX-2 inhibitors in the incidence of acute interstitial nephritis.

NSAID-induced acute tubulo-interstitial nephritis is formally diagnosed by renal biopsy. A patchy acute tubular damage coexists with tubulo-interstitial infiltrate predominantly of T-lymphocytes and, to a lesser extent, monocytes/macrophages, B lymphocytes, plasma cells, and eosinophils [57, 65]. Rarely, a granulomatous interstitial nephritis is seen [66]. Immunofluorescence microscopy is usually negative or nonspecific. The predominance of T-lymphocytes in the interstitial infiltrate has been taken to indicate that T-lymphocyte activation mediates this syndrome, rather than a humoral mechanism, as seen in other forms of drug-induced acute interstitial nephritis [56, 57]. Inhibition of renal COX has also been incriminated in the genesis of NSAID-induced acute tubulo-interstitial nephritis. The resulting stimulation of the lipoxygenase pathway of arachidonic acid metabolism produces leukotrienes, which are potent chemotactic factors for lymphocytes. Recovery of renal function may be only partial [65], and chronic interstitial fibrosis may progress to chronic renal failure [67]. Prednisolone has been successfully used in anecdotal reports, but there is no conclusive evidence that corticosteroids hasten the resolution of the renal lesion [2].

Glomerulonephritis

Membranous nephropathy with nephrotic syndrome may occur as an idiosyncratic reaction to various classes of NSAIDs [68–70]. The temporal association with the intake of NSAIDs, the prompt and complete recovery after drug discontinuation, and the absence of recurrent disease may help distinguish NSAID-associated membranous nephropathy from the idiopathic form [71]. As with NSAIDs, glomerulopathies with the nephrotic syndrome can occur with COX-2 inhibitors [63]. Membranous nephropathy with acute interstitial nephritis secondary to celecoxib has been described [58].

Renal Papillary Necrosis

Renal papillary necrosis has been infrequently reported in patients treated with ibuprofen, indomethacin, phenylbutazone, fenoprofen, or mefenamic acid [51, 67, 72–74] or with paracetamol [75, 76]. One case of celecoxib-related renal papillary necrosis has been reported [77].

Chronic Kidney Disease

Sandler et al. evaluated the risk for chronic kidney disease associated with regular use of nonaspirin NSAIDs in 554 patients with newly diagnosed chronic renal dysfunction [5].

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They found a twofold-increased risk for chronic kidney disease in patients with a history of previous daily use of NSAIDs (adjusted odds ratio [OR] 2.1, 95% CI 1.1–4.1). The increased risk was predominantly limited to men older than 65 years, for whom the OR was 10.0 (95% CI 1.2–82.7) after adjusting for use of other analgesics. The NSAID-associated risk was also greater among those with a history of conditions that might indicate an enhanced susceptibility to the effects of NSAIDs, including previous myocardial infarction, congestive heart failure, heavy alcohol consumption (as a surrogate for cirrhosis), or diuretic use. These observations were confirmed in a case-control study of 716 patients with end-stage renal failure and 361 controls [6]. In this study, a high cumulative intake of NSAIDs (>5000 tablets) was associated with a 4.5-fold excess risk of end-stage renal failure, although the CI was wide (1.0–19.5) and, curiously, this excess risk was not seen when an average annual intake of NSAIDs was examined. Other studies of NSAID usage in hospitalized patients [78, 79] and also cohort studies, however, did not show this association [80, 81]. The reasons for these discrepant findings are unclear. On balance, it seems likely that chronic NSAID use may be associated with a slightly increased risk for the development of chronic kidney failure. Some patients with chronic kidney failure rely on prostaglandin-mediated vasodilatation to maintain renal blood flow [82–84]. Addition of NSAIDs may cause further deterioration of renal function [49, 82, 84, 85].

Salt and Water Retention

NSAID therapy may aggravate the sodium retention induced by renal hypoperfusion in heart failure, cirrhosis, or nephrotic syndrome [3]. Hyponatremia may occur if water retention is disproportionate to sodium retention [86], especially when thiazide diuretics are given simultaneously [2].

Hypertension

Two large meta-analyses encompassing more than 90 studies have demonstrated that NSAIDs may increase blood pressure, especially in previously hypertensive patients [87, 88]. NSAIDs elevate supine mean blood pressure by 5 mmHg [88], a rise known to increase hypertension-related morbidity and mortality [89]. This complication is of importance in the elderly, who are frequently prescribed NSAIDs for musculoskeletal disorders and also have a high prevalence of other chronic disorders, including hypertension.

Whelton et al. performed a post hoc analysis on the renal safety of celecoxib, incorporating more than 50 clinical studies with more than 13 000 subjects [23]. The most common events, peripheral edema (2.1%), hypertension (0.8%), and exacerbation of preexisting hypertension (0.6%), were not dose or time-related. Their incidence and profile were similar to those of nonselective NSAIDs. A similar post hoc analysis of rofecoxib revealed peripheral edema in 3.8% of patients [90].

Whelton et al. also compared the effects of celecoxib at 200 mg and rofecoxib at 25 mg over a 6-week period in 810 hypertensive patients with osteoarthritis, aged over 65 years [91]. Edema developed in nearly twice as many rofecoxib-treated than celecoxib treated patients (9.5% vs. 4.9%, $P = 0.014$). Systolic blood pressure increased significantly in 17% of rofecoxib-treated patients, compared with 11% of celecoxib-treated patients ($P = 0.032$). In conclusion, celecoxib induces edema less frequently and results in smaller rises in blood pressure than rofecoxib. A meta-analysis of COX-2 inhibitors and their effects on blood pressure showed that they were associated with a nonsignificant higher risk of causing hypertension compared with placebo (RR 1.61, 95% CI 0.91–2.84) or nonselective NSAIDs (RR 1.25, 95% CI 0.87–1.78) [92]. Thus, both NSAIDs and COX-2 inhibitors can raise blood pressure, especially in hypertensive, elderly patients, and there is no substantial evidence to suggest that COX-2 inhibitors are safer in this respect.

Pavlicevic et al., in a prospective clinical study, investigated 88 hypertensive patients being treated with lisinopril/hydrochlorothiazide and amlodipine. The effects of addition of ibuprofen, acetaminophen, or piroxicam were recorded over a 3-month period. A significant systolic blood pressure increase of 7.7–9.9% ($P < 0.001$) was reported when ibuprofen and piroxicam were also given with lisinopril/hydrochlorothiazide and NSAIDs [93].

Hyperkalemia and Hyporeninemic Hypoaldosteronism

NSAIDs may cause hyperkalemia, and this is seen more commonly in patients with chronic kidney failure, diabetes mellitus, and type IV tubular acidosis through previously outlined mechanisms [39, 94]. Increases in potassium levels are also expected to occur with COX-2 inhibitors. Indeed, rofecoxib raises serum potassium levels by more than 0.8 mM, with a similar incidence as NSAIDs [95]. In a retrospective cohort study of 202 patients using propensity scores methods the incidence of hyperkalemia was compared between nonselective NSAIDS versus COX-2 selective NSAIDs. Compared to

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patients prescribed nonselective NSAIDs, those prescribed a selective COX-2 inhibitor had a higher risk of serum potassium increase greater than 5 mEq/l (OR 2.56, 95%CI 1.03–6.36). The use of NSAIDs in particular COX-2 inhibitors should be avoided in patients at risk for hyperkalemia and in patients taking other drugs known to decrease renal potassium excretion, such as potassium-sparing diuretics, angiotensin-converting enzyme inhibitors, and β-blockers.

Therapeutic Use of NSAIDs in Nephrotic Syndrome

NSAIDs reduce proteinuria in patients with nephrotic syndrome [40, 96], probably by reducing renal blood flow and glomerular filtration rate [97]. The occurrence of irreversible kidney failure in patients with a nephrotic syndrome treated with NSAIDs [55] suggests great caution for the use of these drugs in this clinical setting.

Conclusions

The increasing use of NSAIDs both by prescription and over the counter has increased the prevalence of nephrotoxicity. A history of NSAID use should be sought in all patients with unexplained impairment of renal function and/or proteinuria. In patients with volume depletion or decreased organ perfusion, the use of NSAIDs should be avoided. NSAIDs should not be prescribed in patients with chronic renal impairment or with a functioning kidney transplant. Patients with an NSAID-induced, interstitial nephritis or papillary necrosis should not be given NSAIDs again. In some individuals who have developed NSAID-induced acute kidney failure and who have recovered kidney function, NSAIDs may be reintroduced if clinically necessary, provided that the risk factors for enhanced susceptibility have been corrected and that renal function is closely monitored. COX-2-selective inhibitor use requires the same cautions as with traditional NSAIDs.

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Part 4

Secondary Diseases of the Kidney

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Hypertension

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Introduction

The kidneys are inextricably interwoven with high blood pressure (BP). In his second paper published in 1836, while describing the natural course of nephritis, Richard Bright mentions the observation of a hard pulse along with a detailed description of the accompanying headache, loss of vision, seizures, and dyspnoea [1]. These cardiovascular changes were then thought to be secondary to the kidney disease, though it is reported that Bright acknowledged the possibility of reverse causation. He did suggest that the "altered quality" of the blood in renal disease affected the peripheral vasculature in such a way that an increased force was necessary for propelling the blood, a remarkably accurate observation. In 1856, Ludwig Traube reasoned that a shrunken kidney will first decrease the amount of liquid which is removed from the arterial system as urinary secretion, as a result of which the pressure of the arterial system ("Aortenspannung") must increase, as good a description of renal parenchymal hypertension as one could have done at the time [1]. BP measurement became more feasible in the late nineteenth century, and in 1874 Mahomed described high arterial pressure which was present before albuminuria in patients with Bright's disease, and advanced the view that high BP could be leading to contracted kidneys [1]. Thus, right from the beginning, hypertension as a cause, or a consequence of kidney disease has been a matter of contention.

Why Treat Hypertension?

Hypertension is called the silent killer in the lay media precisely because it is asymptomatic for the vast majority. As portrayed in the prevention paradox also, the majority of the adverse outcomes may indeed occur in the low to intermediate risk, asymptomatic individuals [2]. Whether it is labeled as a disease or a condition, the global burden of hypertension is high, estimated at 20 526 per 100 000, with significant associated attributable mortality and disability [3]. Thus, treatment of hypertension, i.e. lowering of BP, would be to prevent adverse clinical outcomes. For patients with chronic kidney disease (CKD), these could be either cardiovascular or renal outcomes. Though BP is often bandied about as the most important risk factor for worsening kidney function, the evidence for lowering BP and decreasing progression of kidney disease is rather limited. It is true that at very high levels of BP there exists an association of BP and kidney outcomes. However, in the modern era where the decisions are more to do with whether systolic BP should be lowered to <140, <130 or even to <120, the outcomes that matter are mostly the cardiovascular rather than renal. The relationship of BP with cardiovascular (CV) outcomes is stronger than for progression of kidney disease. Hence, unsurprisingly, lowering of stroke and heart failure drives most of the CV outcome reduction with intensive BP lowering, and prevention of end stage kidney disease (ESKD) is not one of them [4].

Blood Pressure Measurement

An underappreciated aspect of the management of hypertension is proper BP measurement. Inaccurate measurement will result in inappropriate treatment. While the research gold standard of BP measurement is intra-arterial continuous BP monitoring, several practical alternatives are suitable for use in clinical practice. A "casual" measurement performed in a noisy atmosphere using improper

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technique and with inadequate rest is perfectly useless and should be abandoned [5]. At the other end, we have 24-hour ambulatory blood pressure monitoring (ABPM) which provides multiple measurements throughout the day and night, thus providing an assessment of the overall BP load, diurnal pattern, and an assessment of out of office BP values. However, it is not available in all jurisdictions, and cost as well as logistics may hinder universal adoption. A properly done resting office measurement can go a long way, but manual methods are notoriously unreliable, with human error, poor technique, terminal digit preference, and such issues being an unsurmountable barrier despite educational efforts [6]. Automated oscillometric blood pressure (AOBP) offers a suitable compromise, especially newer devices which can specify a period of rest before initiating measurement and with repeat measurements providing an average of two to five readings [7, 8]. Comparative data suggests AOBP use decreases the misdiagnosis of white coat hypertension and, more importantly, it approximates proper resting BP measurement (as is done in clinical trials) more than a casual measurement [7]. Recent hypertension trials, including Heart Outcomes Prevention Evaluation – 3 (HOPE-3), Action to Control Cardiovascular Risk in Diabetes (ACCORD) and the Systolic Blood Pressure Intervention Trial (SPRINT) all used a form of AOBP, and further validation of AOBP with clinical outcomes should be considered hence unnecessary [9–11]. Nevertheless, AOBP should not be construed as a replacement for ABPM. The ABPM can allow for diagnosis of masked hypertension, nocturnal dipping pattern, and provide an assessment of variability.

Another out-of-office technique is home BP measurement. Modern home BP devices use an oscillometric technique, and are cheap and easy to use. They offer similar advantages to the ABPM method, in providing multiple measures for an overall BP load, potentially minimizing white coat effect and picking up masked effect. Caveats of home BP measurement include the accuracy of these devices, as multiple studies have reported a large proportion of home BP monitors being inaccurate [12, 13]. Lastly, they do not provide a picture of nocturnal pattern and variability as ABPM does. They do, however, empower patients, and have been reported to result in improved BP control, potentially by overcoming therapeutic inertia [14].

Wearable BP devices are the next frontier, with one device being approved recently in the United States. Potentially, these will provide richer data about BP and empower patients immensely. Certain caveats about their accuracy and the ability to deal with the sheer amount of information and possible resultant false alarms will have to be worked out before widespread adoption [15].

To summarize, out-of-office measurement, preferably with ABPM followed by home BP measurement, is the preferred way of diagnosing and following up hypertension management. Office measurement with AOBP is a reasonable alternative when this option is not routinely available. Table 22.1 provides highlights of different BP measurement techniques.

Table 22.1 Different BP measurement methods and their advantages and disadvantages.

Technique	Advantages	Disadvantages	Comments
Casual	Easy	Rarely done correctly Misdiagnosis of true BP	Should be abandoned
AOBP	Eliminates many human errors Can specify rest period Multiple measurements Minimizes white coat effect	More time required Workflow may be slowed Cannot diagnose masked hypertension or diurnal pattern	Used in recent trials Devices vary with respect to period of rest, number of measurements
ABPM	Diagnose white coat and masked effect Assess BP variability Assess nocturnal BP pattern Assess overall BP load	Cost Inconvenience	"Gold standard" Strong association with outcomes Outcome trial with ABPM-based strategy ongoing
Home	Inexpensive Easy Can diagnose white coat and masked effect Empowers self-management	Accuracy variable Cannot assess nocturnal pattern	

AOBP, automated oscillometric blood pressure; ABPM, ambulatory blood pressure monitoring; BP, blood pressure.

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Blood Pressure Variability

A brief note about BP variability is necessary given its reported association with clinical outcomes. Though we still do not know enough about the causes and the cure, we do know more about the consequences of high BP variability. Variability is variably defined based on the time frame. Short-term variability refers to that seen on a 24-hour ABPM whereas long-term refers to visit-to-visit variability. Numerically, variability is often defined on the basis of a large standard deviation or a coefficient of variation that reflects an overall dispersion of the values around the mean, but not specifically the order of these dispersed values. The average real variability represents a potentially more reliable representation of true variation [16]. Long-term variability refers to visit-to-visit variation, as measured on the basis of office or out-of-office measurements. An increased short-term, as well as long-term, variability is associated with a correspondingly increased risk of cardiovascular events. Specifically in CKD, visit-to-visit variability has been reported to be associated with a 20% higher relative risk of death and a 90% higher risk of hemorrhagic stroke (though with no association for ischemic stroke, heart failure or ESKD) [17]. Similarly, CKD itself has been associated with short-term variability, with the caveat that the absolute variability may seem higher in CKD purely because individuals with CKD are more likely to have higher BPs [18]. Certain extreme cases are caused by autonomic dysfunction; however in the vast majority we still do not have a good mechanistic explanation of this phenomenon. Additionally, a search for strategies that could potentially mitigate this variability and whether these will also reduce the higher risk of adverse outcomes is fertile ground for clinical research.

Nocturnal Pattern

The normal pattern of BP has a diurnal variation with lower BP at night and a fall of about 15% being commonly observed [19]. The absence of this nocturnal dipping is defined as an average nocturnal systolic BP being 10% or more lower than the daytime average. This absence of nocturnal dipping (i.e. being a "nondipper") is associated with an increased risk of cardiovascular events and mortality in the general population. In the CKD literature, the effects are less clear, since nondipping is also associated with other comorbid conditions (e.g. diabetes, proteinuria) which are themselves also associated with poor outcomes, thus making causation somewhat confounded [20]. An exception is a study from Italy, which did take proteinuria and comorbidities into account and reported an increased hazard of death and ESKD amongst nondippers compared to dippers [21].

The prevalence of nondipper status is quite high in CKD, with reports estimating it at 60–80%. Mechanistically, absence of nocturnal dipping is thought to be caused by heightened sympathetic activity, increased sodium sensitivity and volume status, and disturbances of the sleep activity cycle. These factors are all clearly more common in CKD patients, thus the finding of increased nondipping is not surprising. More important is whether nondipping status can be corrected and whether this correction decreases the adverse risk profile observed in these patients.

One group has reported success with nighttime dosing of BP medications in CKD patients, which lowered nocturnal BP sufficiently to restore normal dipping pattern in an additional 30% of the patients compared to controls, but also resulted in an improved survival [22]. Interpretation of these fantastic results (which reported a hazard ratio of 0.28 for major adverse cardiovascular events [MACEs]) from the Monitorización Ambulatoria de la Presión Arterial y Eventos Cardiovasculares, i.e. the Ambulatory Blood Pressure Monitoring and Cardiovascular Events (MAPEC) study, should be tempered with the lack of effect on nocturnal BP seen in two other trials [23]. Moreover, the reduction in MACE outcomes reported in the MAPEC study with bedtime dosing (but not additional BP lowering medications) is higher than the reduction reported in the HOPE study with ramipril compared to placebo (hazard ratio [HR] 0.28 in MAPEC and HR 0.78 in HOPE) [20]. Nevertheless, bedtime dosing is a simple and inexpensive intervention that could be applied to most BP lowering drugs with the exception of diuretics.

Since sleep apnea is associated with nondipping status, correction of sleep apnea with a device such as continuous positive airway pressure (CPAP) could presumably lower nocturnal BP. From a meta-analysis of four randomized controlled trials (RCTs), the effect of CPAP therapy was quite small on nighttime BP, with a mean reduction of 1.9 mmHg in systolic BP and 1.5 mmHg in diastolic BP, insufficient to significantly alter dipping status [24]. Not surprisingly, CPAP therapy has also failed to show a benefit overall for MACE or mortality, though other benefits, especially on sleep quality and quality of life, do exist [25].

Masked Hypertension

Masked hypertension deserves a separate mention since it follows, as a corollary of improper BP measurement, that it is underrecognized and potentially undertreated. Masked effect, in general, refers to an out-of-office BP measurement that is *higher* than the office measurement. Masked hypertension refers to the phenomenon when BP may be normal (or controlled) in the office, but elevated out of office. An additional wrinkle is whether this masked hypertension is present, but controlled, or uncontrolled. See Table 22.2 for a breakdown of the somewhat bewildering terminology. The

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Table 22.2 Different facets of masked hypertension with a proposed labelling scheme.

Possible label	Normotension	Masked effect	Masked, untreated hypertension	Masked uncontrolled hypertension	Masked controlled hypertension
Office BP	Normal	Normal	Normal	Normal	Normal
Out-of-office BP	≤10 mmHg of office BP	>10 mmHg of office BP	>10 mmHg of office BP	>10 mmHg of office BP	>10 mmHg of office BP
Out-of-office BP controlled?	Yes	Yes	No	No	No
On treatment?	No	No	No	Yes	Yes
Possible label	Normotension	Masked effect	Masked, untreated hypertension	Masked uncontrolled hypertension	Masked controlled hypertension

BP, blood pressure.

exact biological explanation for this phenomenon is not satisfactorily elucidated yet, though observational studies suggest associations with age, sex, increased sympathetic activity, and certain personality types [26].

This phenomenon matters in CKD because the prevalence of masked hypertension in CKD is higher than in the general population. Most reports peg the prevalence at about 20–30% with slightly higher numbers (43–50%) reported in two cohorts with a high proportion of African-American individuals [21, 27–33]. More important than mere prevalence numbers is whether masked hypertension is associated with adverse outcomes. Masked hypertension is indeed associated with surrogate outcomes such as increased left ventricular mass index and proteinuria, and also with a higher risk of cardiovascular outcomes (see Table 22.3 for a summary of the reported literature). Perhaps even more clinically relevant is whether treatment of masked hypertension mitigates the risk of these adverse outcomes or just represents a more aggressive phenotype with the masked hypertension being an epiphenomenon? An ongoing randomized trial, the MASTER trial (MASked-unconTrolled hypERtension Management Based on Office BP or on Out-of-office, Ambulatory BP Measurement; NCT02804074) might fill some of these lacunae, randomizing 1240 patients to an office versus ABPM guided strategy. The sample size is powered for surrogate outcomes (albuminuria and left ventricular mass index) and not hard clinical outcomes, nevertheless it will be helpful to validate the practice of diagnosing and treating masked hypertension.

Treatment of Hypertension in CKD

Nonpharmacological Measures

Nonpharmacological measures that have been reported to be efficacious in hypertension include changes in diet (less sodium, more potassium, and other dietary interventions), more exercise and weight loss, and lower alcohol intake. These are well-established interventions on the basis of RCTs and systematic reviews of RCTs, mostly in the general population. Most of these can be extrapolated to the CKD population, with a few considerations, as summarized in Table 22.4 [34, 35].

Sodium: A good systematic review from the World Health Organization (WHO) reports a reduction in BP of about 3.4 mmHg in systolic BP and 1.5 mmHg in diastolic BP in trials of reducing sodium intake [36]. The mean reduction of sodium intake in these trials was an impressive 1.7 g/day (45% from baseline). Though these trials were in the general population, one could presume that the contribution of sodium intake to hypertension would be even higher in the CKD population. One small RCT from Australia of 20 patients did report a significant decrease in BP with sodium restriction, of −10/4 mmHg, in patients with CKD (glomerular filtration rate [GFR] 15–59 ml/min) [37]. Another small crossover RCT of 58 patients with stage 3 or 4 CKD also reported a decrease of 10.7 mmHg in 24-hour ABPM, accompanying a 57 mmol decrease in 24-hour urinary sodium and a mean weight loss of 2.3 kg [38].

Potassium: Another WHO systematic review highlighted the evidence that increasing potassium intake (whether by diet or by using a supplement) also resulted in lower BP, on the order of −3.5 mmHg in systolic BP and −2.0 mmHg in diastolic BP [39]. Increasing potassium intake, needless to say, should be done more carefully and extrapolating to CKD, especially advanced CKD, where there might be a limit to the tubular potassium excretion, may not be wise. An ongoing RCT of a potassium supplement (40 mmol of potassium chloride, potassium citrate or placebo) in 400 patients with advanced CKD (GFR 15–44 ml/min) will provide more data on the efficacy and safety of potassium in the CKD population [40].

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Table 22.3 Estimates of masked hypertension in the literature and the association with clinical outcomes.

		Prevalence of ABPM profiles		
		Normotension/ controlled hypertension	Masked uncontrolled hypertension	
Study	**Cohort details**	**White coat hypertension**	**Sustained hypertension**	**Comments**
Pogue et al. (AASK) [28]	$n = 617$ 100% Black 0% diabetes Mean age 60 years 62% men Mean GFR 44 ml/min/1.73 m^2 29% proteinuria[1]	37% 2%	43% 18%	Masked and sustained hypertension associated with LV hypertrophy and proteinuria
Gorostidi et al. [27]	$n = 5693$ 0% Black 33% diabetes Mean age 67 years 58% men Mean GFR 56 ml/min/1.73 m^2 5% proteinuria[2]	15% 29%	7% 50%	
Iimuro et al. [155]	$n = 1057$ 0% Black 35% diabetes Mean age 61 years 63% men Mean GFR 29 ml/min/1.73 m^2 89% proteinuria[3]	38% 6%	31% 26%	
Minutolo et al. [156]	$n = 489$ 0% Black 36% diabetes Mean age 64 years 59% men Mean GFR 45 ml/min/1.73 m^2 Mean proteinuria 0.3 g/day	17% 22%	15% 47%	Masked and sustained hypertension associated with mortality, dialysis and cardiovascular events
Drawz et al. (CRIC study) [30]	$n = 1492$ 39% Black 42% diabetes Mean age 63 years 56% men Mean GFR 46 ml/min/1.73 m^2 50% proteinuria[2]	49% 4%	28% 19%	Masked and sustained hypertension associated with greater LV mass index
Agarwal et al. [31]	$n = 333$ 17% Black 66% diabetes Mean age 69 years 98% men Mean GFR 44 ml/min/1.73 m^2 Mean ACR 0.33 g/g	10% <1%	50% 39%	

(*Continued*)

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Table 22.3 (Continued)

		Prevalence of ABPM profiles		
		Normotension/ controlled hypertension	Masked uncontrolled hypertension	
Study	**Cohort details**	**White coat hypertension**	**Sustained hypertension**	**Comments**
Wang et al. [32]	$n = 588$ 0% Black 16% diabetes Mean age 43 years 57% men Mean GFR 68 ml/min/1.73 m^2 Mean proteinuria 1.7 g/day	25% 10%	21% 45%	Masked and sustained HT associated with greater mortality, CV and renal events
Kushiro et al. (HONEST study) [33]	$n = 4346$ 0% Black 29% diabetes Mean age 71 years 50% men Mean GFR 51 ml/min/1.73 m^2	38% 9%	29% 24%	Masked, white coat and sustained HT associated with greater CV events
Scheppach et al. [157]	$n = 300$ 0% Black 24% diabetes Mean age ~58 years 60% men Mean GFR ~ 51 ml/min/1.73 m^2	41% 11%	18% 30%	Increased LV mass index (white coat, masked and sustained hypertension) Increased PWV (masked and sustained HT)

AASK, African American Study of Kidney Disease; ACR, albumin to creatinine ratio; CRIC, Chronic Renal Insufficiency Cohort study; GFR, glomerular filtration rate; HONEST, Home BP measurement with Olmesartan Naive patients to Establish Standard Target blood pressure; LV, left ventricular.

Table 22.4 Major nonpharmacological measures in management of hypertension in CKD.

Intervention	Expected BP decrease	Evidence in CKD?	Comments
Sodium reduction	−3.4/1.5 mmHg	Yes	Small RCTs in CKD suggest greater BP lowering (~10 mmHg)
Potassium increase	−3.5/2.0 mmHg	No	Risk of hyperkalemia Await ongoing RCTs
Alcohol reduction	−5.5/4.0 mmHg	No	Little reason to doubt heterogeneity in CKD
Exercise	−4.6/2.6 mmHg	Yes	Small trials, adherence, effectiveness unknown
DASH diet	−11.4/5.5 mmHg	No	Small feeding RCT of $n = 11$ Observational data suggests benefit

BP, blood pressure; CKD, chronic kidney disease; DASH, Dietary Approach to Stop Hypertension; RCTs, randomized clinical trials.

DASH diet: The Dietary Approach to Stop Hypertension (DASH) trial demonstrated a robust reduction in systolic BP of 11.4 mmHg and diastolic BP of 5.5 mmHg [41]. The DASH diet consists of eating vegetables, fruits, and whole grains, including fat-free or low-fat dairy products, fish, poultry, beans, nuts, and vegetable oils, limiting foods that are high in saturated fat, such as fatty meats, full-fat dairy products, and tropical oils such as coconut, palm kernel, and palm oils, and limiting sugar-sweetened beverages and sweets. Of interest in CKD, the DASH diet provides approximately 4700 mg potassium corresponding to about 120 mmol/day. A small feeding trial of 11 patients with

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CKD did not demonstrate a significant increase in serum potassium (+0.15 ± 0.28 mmol/l) [42]. Longer-term data are not available. Observational data suggest an association between following the DASH pattern of diet and slower decline of kidney function [43], but there are no RCTs which support such an effect. Caution should be exercised in recommending the DASH diet in patients who may have high normal potassium or being concomitantly started on other agents such as renin angiotensin system (RAS) blockade.

Alcohol: Despite robust epidemiological data supporting the association of higher alcohol intake and BP, most public health messages do not mention temperance as a means of lowering BP. These data are actually now bolstered with high-quality trials which show that reduction of alcohol intake results in a lowering of BP, with an overall effect of −5.5/−4 mmHg for systolic and diastolic BP [44]. Moreover, this meta-analysis also demonstrated a dose–response effect, with the strongest effect seen in those who drank more than six drinks and no significant reduction in BP seen from further reduction in those who drank two or fewer drinks per day.

Exercise: Evidence from the general population supports a recommendation to exercise in an effort to decrease BP. Specifically, a systematic review of 21 trials reported that a supervised program of aerobic exercise of 30–60 minutes, five times per week, can reduce systolic BP by a pooled estimate of 4.6 mmHg and diastolic BP by 2.6 mmHg [45]. In addition, we do have data in CKD patients from a systematic review which reported the effects of exercise (including cardiovascular training, mixed cardiovascular and resistance training, resistance-only training, and yoga) [46]. The review reports a similar overall reduction in BP (mean difference, 6.1 mmHg in systolic from nine trials and 2.3 mmHg in diastolic from 11 trials) as the previous review conducted in the general population. However, in subgroup analyses, the effects were significant in the pooled analysis of trials when exercise training was supervised (and was not significant in trials when it was unsupervised) and in trials with high-intensity exercise training (and not significant in trials with low-intensity exercise). Lastly, emerging data also suggest that the beneficial effect of exercise on BP is not restricted to aerobic, but also to dynamic resistance and isometric static exercise [47, 48].

Stop Interfering substances: Interfering substances which can increase BP include prescription drugs such as nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, erythropoiesis-stimulating agents, antidepressants, methylphenidate, and over-the-counter remedies such as cough/cold/allergy preparations, appetite suppressants, licorice and drugs such as cocaine.

Efficacy and Effectiveness in Nonpharmacological Interventions

Several caveats should be taken into account when considering nonpharmacological interventions for management of hypertension in CKD. Indeed, patients often favor lifestyle modifications and shy away from starting BP lowering medications, demonstrating pill disutility, sometimes of an extreme nature [49]. In situations when the observed BP is ~5 mmHg higher than the target, and in a motivated patient, it is indeed reasonable to focus on lifestyle changes and review at the next visit. However, effects seen in RCTs are likely to be an overestimate of the effects one might see in real clinical practice. RCTs of diet in the hypertension literature are feeding trials (and are not trials of counseling) and as mentioned in the exercise section, the exercise interventions that have the most effect are supervised interventions [50]. A healthier diet is more expensive (estimated at ~US $1.5 daily) [51]. Access to resources and care, attention to adherence, and physician–patient interaction are all additional determinants of true effectiveness. A neglected area, which is especially important for complex interventions such as lifestyle change, is poor health literacy, which is especially common in CKD [52–54]. In the setting of poor health literacy, pharmacological therapy may be considered preferable to these complex and often costly lifestyle changes.

Level and Drug Choice

Over the last few decades, the research has shifted from whether high BP should be lowered at all, to how should it be lowered, and now to how low should it be lowered [55, 56]. With respect to first-line drug to use in hypertension, the seminal trial in the primary care population was the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), which reported that a thiazide-like diuretic (i.e. chlorthalidone) was superior to alpha-adrenergic antagonists (doxazosin) and just as good as an angiotensin converting enzyme inhibitor (ACE-I, lisinopril) or a calcium channel blocker (CCB, amlodipine) [57]. This and other evidence have lead to the acceptance of one of the so-called A-C-D drugs (i.e. ACEi or angiotensin receptor blocker [ARB], a CCB, or a diuretic) as the choice for first-line BP lowering drug, as well as being the first three drug classes that should be used for BP lowering. These drugs are also the ones to be preferably combined when one drug is not enough, as is common in CKD.

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With respect to the level of BP control, BP control down to 140/90 has been widely accepted. Beyond that, to what is labeled as "intensive BP lowering", to systolic BP levels of <120 or <130, is still a matter of contentious debate, and is discussed below.

Pharmacotherapy

Nonpharmacological measures are insufficient for BP lowering in most CKD patients, most of whom need pharmacotherapy not just for BP lowering, but in addition for specific indications such as the antiproteinuric effect or more specifically for CV protection. A large cohort study suggests that about 60% of CKD patients receive three or more antihypertensive medications, thus making the discussion of the specific BP lowering class somewhat redundant [58]. The discussion below summarizes some of the evidence of the specific medications, while acknowledging that combination therapy with most of the first-line drugs will be the most common scenario.

Renin Angiotensin System Blockade

RAS blockade, consisting of either ACEi or angiotensin receptor blockade (ARB), has become a mainstay of hypertension management in CKD. ACEi blocks the conversion of angiotensin I to angiotensin II, a potent vasoconstrictor, and ARBs block the angiotensin II receptors. The downstream reduction in aldosterone secretion and sodium reabsorption, coupled with a decrease in angiotensin II medicated vasoconstriction, underlies their BP lowering effect. Extensive trial data demonstrate the benefit in CV outcome reduction with these agents. However, a careful examination of how much of their effect is independent of BP lowering reveals a slightly complicated story. Briefly, when compared against placebo, RAS blockade is indeed superior in preventing CV outcomes and prolonging survival. However, when compared against active comparators, i.e. other BP lowering drugs, then there is no significant difference for hard clinical outcomes in patients with heart disease, or with diabetes, or with nonproteinuric CKD. The major factor in all these systematic reviews is the inclusion of ALLHAT, which did not report a benefit to using lisinopril over chlorthalidone and, being a large trial, carries a lot of weight in the meta-analysis [59]. The only exception, where RAS blockade is clearly superior to other BP lowering drugs, is in the setting of proteinuric diabetic nephropathy. RAS blockade has an additional effect on the intraglomerular pressure by dilatation of the efferent arteriole, reducing proteinuria and explaining this additional beneficial effect. However, one might consider this as an academic question, since most CKD patients do require more than one agent, and RAS blockade being part of that armamentarium is eminently sensible.

What is not sensible is the use of an ACEi and an ARB in combination. In patients at high CV risk, and in patients with proteinuric diabetic nephropathy, the use of these in combination did not demonstrate any benefit in CV or kidney outcomes [60, 61]. Moreover, there was an excess risk of hyperkalemia and acute kidney injury, and since then dual RAS blockade has not been recommended for use in management of hypertension. Lastly, the direct renin inhibitor aliskiren might have similar effects as ACEi or ARB. However, the major clinical trials were all conducted in combination with either an ACEi or an ARB, and as with ACEi–ARB combination, these did not demonstrate any benefit and increased risk of adverse events [62]. Monotherapy with aliskiren might have similar effects as ACEi or ARB monotherapy, but this has not been proven and hence aliskiren use may be relegated to the rare occasion when RAS blockade is desirable, but both drugs are not tolerated.

Thiazide and Thiazide-like Diuretics

Thiazide diuretics are the oldest class of BP lowering drugs which are still first-line agents. They act on the NaCl transporter in the distal convoluted tubule and acutely do cause natriuresis. With chronic therapy, however, extracellular volume comes back to baseline but peripheral resistance falls, from an unknown mechanism, but thought to be related to the initial natriuresis. The main thiazide diuretics are hydrochlorothiazide (HCTZ), Bendroflumethiazide, and chlorothiazide. The thiazide-like diuretics, namely indapamide and chlorthalidone, are somewhat longer acting, have greater effect on nocturnal BP, and are more potent compared to HCTZ, the most commonly used thiazide [63]. Moreover, in the RCTs that demonstrate a benefit with diuretics, either chlorthalidone or indapamide have been used [10, 57, 64]. Even in SPRINT, chlorthalidone was preferentially used in the formulary. Some other RCTs in which HCTZ has been used have failed to report beneficial CV effects [9, 65]. However, no head-to-head trial of HCTZ compared to chlorthalidone exists, though one is ongoing [66]. Additionally the increased potency of thiazide-like diuretics can result in more adverse events related to electrolyte imbalances in particular [67]. For relevance to CKD, thiazide diuretics were not thought to be effective in severe CKD (GFR < 30). This has been challenged in a recent pilot trial with chlorthalidone and more data is awaited [68].

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Calcium Channel Blockers

CCBs bind to the alpha-1 subunit of L-type calcium channels, lowering cytosolic calcium and resulting in vascular smooth muscle relaxation and consequent vasodilatation. The nondihydropyridine CCBs (diltiazem and verapamil) also have an additional negative chronotropic effect on the heart. Because of their additional drug interactions (inhibition of the cytochrome p450 3A4 system) and drug interactions, these are used less often compared to the dihydropyridine CCBs, namely nifedipine, amlodipine, and others. These drugs are mostly hepatically metabolized and do not require dose adjustment, have few metabolic adverse effects, and work throughout the spectrum of CKD.

Second-line Drugs

Spironolactone, doxazosin, and bisoprolol all significantly reduced BP compared to placebo, as add-on to the A-C-D combination in patients with resistant hypertension [69]. The highest BP lowering effect was with spironolactone, and this would be the appropriate fourth agent to use in this setting. The trial, however, excluded patients with GFR <45 ml/min, and the efficacy of spironolactone for BP lowering is not well established in severe CKD. A small observational study does suggest it has BP lowering effects below a GFR <45, albeit with the additional unsurprising risk of hyperkalemia [70]. A follow-up of the same Prevention And Treatment of Hypertension With Algorithm-based therapy (PATHWAY) trial also suggested that the efficacy of amiloride may be similar to spironolactone [71]. Eplerenone is another mineralocorticoid antagonist which does not have the androgenic side effects of spironolactone. Alpha- and beta-adrenergic antagonists are the next preferred agents, based on the PATHWAY-2 trial [69]. These suggestions are based on BP lowering and not on clinical outcome data.

Centrally acting alpha-agonists (clonidine and guanfacine) and direct vasodilators (minoxidil and hydralazine) are also potent in BP lowering and reserved for use after exhausting all above options. Clonidine is available in some countries as a transdermal patch, which can be applied once a week (especially useful for hemodialysis patients). Though hydralazine has some evidence (though not in the CKD setting), it requires three to four times a day dosing and minoxidil is preferable for BP lowering.

Newer Agents

Sodium-glucose transporter inhibitors (SGLT2i), which are perceived as hypoglycemic agents, also have natriuretic and BP lowering effects. A meta-analysis reports a lowering of BP by −3.8/−1.8 mmHg with these agents, which also have clinical outcome data in the form of heart failure and CV event reductions [72, 73]. The neprilsyn inhibitor, sacubutril/valsartan, has been reported to improve survival in patients with congestive heart failure [74]. It has been shown to be safe in a recent trial in CKD patients (GFR 20–60) and reduced BP more than irbesartan by about 5 mmHg [75]. Other classes of drugs which show promise in BP lowering and are under investigation include aldosterone synthase inhibitors, ACE-2 activators, aminopeptidase inhibitors, angiotensin Ii vaccines, and endothelin antagonists [76].

Combination Choice

Mechanistic considerations and empiric data, along with pharmacokinetic considerations and adverse effects, are the factors that go into decisions about drug combinations. From a physiological perspective as well as reviewing trial data, combining RAS blockade with either CCB or diuretics makes sense. Conversely, combining a beta-blocker with RAS blockade does not, given that renin release would already be reduced by the beta-blocker. Similarly, combining a CCB with a diuretic has no specific synergistic advantages (and often the diuretic has been mistakenly added to manage CCB-induced leg edema, better treated with a lower dose of the CCB and addition of RAS blockade). For patients with CKD, given the primacy of RAS blockade, combining them with either a diuretic or a CCB makes eminent sense, followed by addition of the third agent. Since the publication of the PATHWAY study, as well as observational data supporting the relatively high prevalence of hyperaldosteronism in this population, a mineralocorticoid antagonist is the ideal fourth agent [69]. Beta-blockers, alpha adrenergic antagonists and vasodilators and central sympatholytic agents come next. Little trial evidence for clinical outcomes exist for these drugs, hence their relegation here. It is not unusual for their use to be common in later stages of CKD, when fears of worsening creatinine have lead to discontinuation of RAS blockade and/or diuretics.

Device Therapy

Device therapy has shown some promising results in recent years, but it is far from being ready for clinical use yet. It is nevertheless important to review the most promising interventions and any potential role they might have for management of hypertension in CKD patients.

Sympathetic renal nerve ablation has the most data among all device-based interventions. We have known that lumbar sympathectomy is extremely effective in

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lowering BP since Adson's first case report decreasing the BP from 250/180 to 170/120 after ventral rhizotomy [77]. However, this procedure was almost always followed by impressive side effects, such as loss of sensation, paralytic ileus, problems with ejaculation, and loss of sweating and the occasional mortality [78]. With the advent of safe BP lowering drugs, sympathectomy went rapidly out of favor. This was the state of affairs until a few years ago, when an intrepid group reported on the role of renal sympathetic nerves in resistant hypertension, followed by the successful demonstration of percutaneous renal denervation using a catheter with a dramatic BP fall [79, 80]. The initial excitement following the first few clinical trials came crashing down to Earth after the release of the Symplicity HTN-3 trial [81]. This was the first sham controlled and double-blind RCT, performed in patients with resistant hypertension, and showed no difference in BP (~14 mmHg decrease in both groups). However, subsequent soul-searching and an awareness of the problems inherent in studying patients with resistant hypertension (with high variance and varying adherence) lead to the design of different RCTs [82]. The resultant RCTs, this time in patients with mild hypertension, reported a decrease of about 5–6 mmHg and this seems to be the true average BP lowering effect of renal denervation [83, 84]. Safety in the short term seems good, though the absence of a renal sympathetic afferent system has been associated rarely with shock and acute kidney injury [85]. Do these results mean renal denervation could help CKD patients? Most CKD patients do require more than one BP lowering medication, so the advantages of reducing pill burden by one (considering the average effect of −5 mmHg) is small. Second, while increased sympathetic activity might indeed have a larger role to play in hypertension in advanced CKD, there is no data on clinical outcomes. Small case series do report that denervation is technically feasible in CKD patients, so the benefits will have to be carefully weighed if denervation becomes widely available [86, 87].

The other device therapies under development include baroreceptor activation and the arteriovenous fistula creation. Baroreceptor activation therapy in theory modulates "deranged sympathovagal balance" but in practice the clinical trial did not meet safety or efficacy endpoints, though further refinements are ongoing [88]. Central iliac arteriovenous anastomosis creation has been reported in a small open-label trial, in which ipsilateral venous stenosis developed in a third of the patients (along with significant BP reductions) [89]. Lack of blinding, lack of data on clinical outcomes, and serious long-term safety concerns suggest this is the least promising of all device-based BP lowering interventions.

Patient Populations

Intensive BP Lowering

RCTs of BP lowering have traditionally been conducted in carefully defined populations based on demographics or comorbidities, e.g. the elderly (Systolic Hypertension in the Elderly Program [SHEP] and Hypertension in the Very Elderly Trial [HYVET]) [64, 90], diabetes (ACCORD) [11], African-American with kidney disease (AASK) [91] and so on. These groups are not homogenous when it comes to CV risk, which is the main purpose of treating hypertension. Hence the benefits (and risks) of BP lowering will vary even within these populations based on their underlying CV risk. On the other hand, stratifying populations based on the underlying CV risk may represent a cleaner view on the risks and benefits of BP lowering, especially of intensive BP lowering. Indeed, a meta-analysis from the BP Treatment Trialists Collaboration does show that there is no heterogeneity on relative risk reduction between trials with and without CKD or diabetes [92]. The common denominator for understanding treatment benefit is the underlying baseline CV risk. As shown in Figure 22.1 from an individual patient level meta-analysis, the absolute risk benefit with BP lowering increases with higher level of baseline CV risk [93]. One proposed scheme to think about stratifying patient population while thinking about intensive BP lowering is shown in Figure 22.2 [56]. Needless to say, intensive BP lowering requires careful assessment of the risk of adverse events, such as electrolyte imbalances and orthostatic hypotension.

Nondiabetic CKD

Four major RCTs have been conducted in nondiabetic CKD with BP lowering targets, as summarized in Table 22.5 [10, 91, 94–96]. As can be seen, the earlier trials were not powered for CV outcomes, nor for all-cause mortality. In one of the trials, the separation between arms of the BP was also minimal. The largest and most consequent RCT in this area is hence the Systolic Blood Pressure Intervention Trial (SPRINT) [10]. In the main trial, there was no significant interaction between the patients with CKD and those without CKD, which is the proper method to assess if patients with CKD are different in their response to intensive BP lowering. In addition, the detailed analysis of the CKD subgroup published subsequently confirms the benefit of intensive BP lowering for all-cause mortality [94]. A subsequent systematic review, including data from 18 RCTs and 15 924 participants confirms these findings, reporting 14% relative risk reduction in mortality with intensive BP lowering

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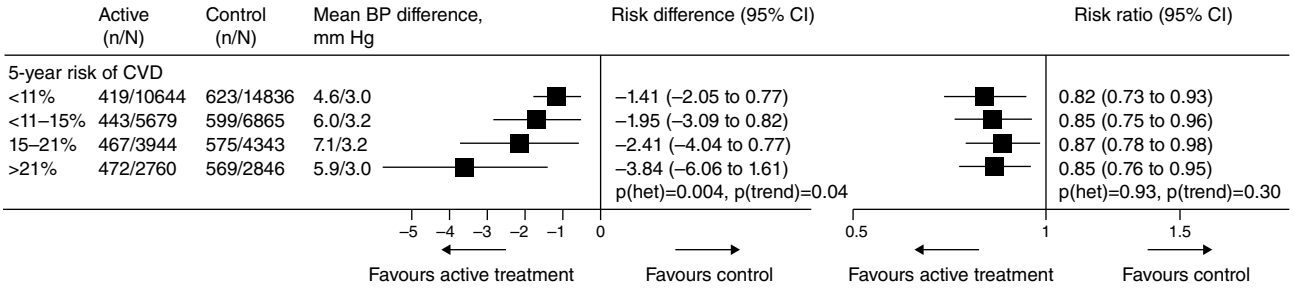

Figure 22.1 Effects of blood pressure reduction on absolute and proportional risks of cardiovascular disease for patient groups defined by different baseline levels of cardiovascular risk. Total sample, *n* = 51 917. *n/N* is the number of cases/number at risk. BP difference is the difference between active and control groups in treatment-induced reduction in systolic/diastolic blood pressures. BP, blood pressure; CVD, cardiovascular disease; Het, heterogeneity. *Source:* From Sundstrom et al. [93] used with permission. © 2014, Elsevier.

(with an achieved systolic BP fall from a mean of 148 to 132 mmHg) [97]. Indeed, the risk of adverse events, mostly electrolyte disorders, do also go up as a consequence of adding potent antihypertensive agents, but this risk should be weighed against the benefit of not dying.

Diabetic CKD

There are no trials which specifically included patients with diabetes and CKD, and targeted a certain BP level intervention. From the general population with diabetes, the most relevant trial is Action to Control Cardiovascular Risk in Diabetes Blood Pressure (ACCORD) [11]. In this randomized trial, 4773 patients with diabetes and at high CV risk were randomized to two BP targets: systolic BP <140 mmHg versus systolic BP <120 mmHg. The overall primary composite outcome was not significantly different between the two groups, with a hazard ratio of 0.88 (95% confidence interval [CI] 0.73–1.06). Of all the specific events included, stroke (which arguably has the strongest link with BP) was significantly lower with the intensive BP target (HR 0.59, 95% CI 0.39–0.89). There was much consternation about the slightly greater number of deaths with intensive BP lowering (150 versus 144, HR 1.07, 95 CI 0.85–1.35). Intriguingly, this has lead to many different post hoc analyses, with two major schools of thought being that either ACCORD was underpowered (the observed event rate was about half as expected) or the other showing an effect modification [98]. ACCORD had a factorial design, with the other intervention being intensive blood glucose lowering, which was found to be harmful compared to standard glucose control [99]. In a post hoc analysis of ACCORD published a decade after the original publication, a significant interaction ($P = 0.03$) was reported, such that in the group receiving standard glucose lowering, intensive BP lowering decreased mortality, whereas in the intensive glycemic control group, intensive BP lowering increased mortality [100]. Thus it is indeed possible that intensive BP lowering not only confers a benefit in stroke reduction, but may not increase mortality if done in conjunction with standard, but not intensive, glycemic lowering.

Another approach, using a Bayesian analytic model of conducting a meta-analysis of *achieved* BP suggests intensive BP lowering is associated with a 10% reduction in all-cause mortality, a 17% increase in stroke, but with a 20% increase in serious adverse effects [101]. Specifically, it also suggests that these benefits were seen with an achieved BP of 130–135 mmHg, with further reductions only providing additional benefit in stroke reduction. These and other meta-analytic approaches either rely on baseline BP or achieved BP for grouping trials and arms [102–104]. They also include RCTs of BP lowering agents (e.g. olmesartan or lisinopril-losartan combination) compared with placebo, where the achieved BP would be higher with placebo, but where the interventions are no longer used as tested in these RCTS (e.g. dual blockade) [60]. To finish this discussion, the most recent meta-analysis of these reports on the CV effect of a standardized decrease of 10 mmHg on outcomes [4]. Overall, they report a benefit of 10 mmHg BP lowering on CV outcomes (including stroke and heart failure) and on all-cause mortality in diabetes, with little heterogeneity between trials in patients with and without diabetes (see Figure 22.3).

These analyses, needless to say, are from the general population, and not in CKD, where we must necessarily extrapolate the evidence. Should we expect outcomes to be different in patients with diabetes and CKD compared to those without CKD? From a mechanistic perspective, patients with diabetes and CKD are possibly different, but from an empiric point of view, no interaction has been reported yet from epidemiological studies.

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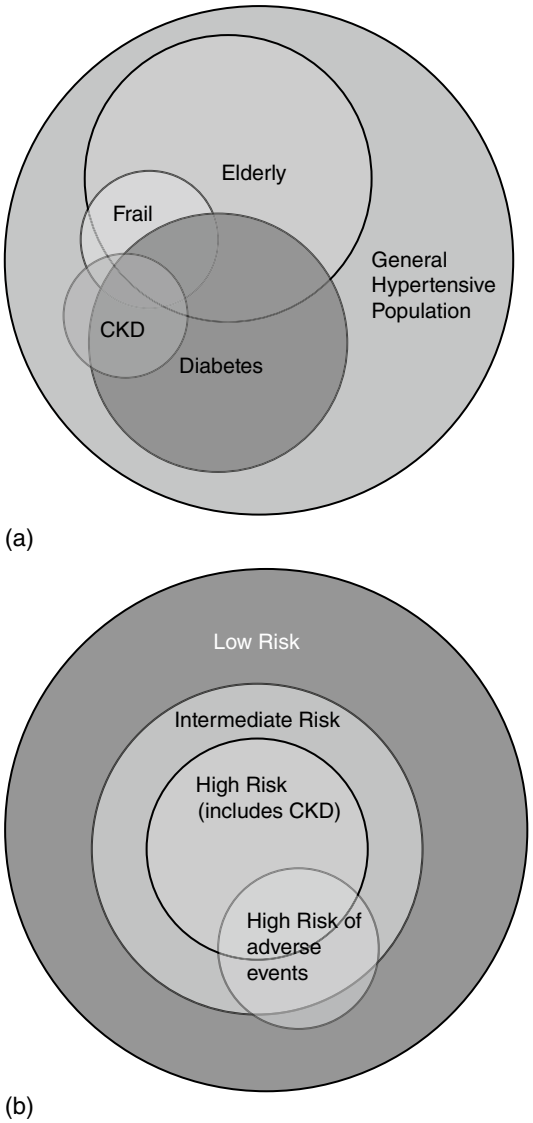

Figure 22.2 (a) This schematic (not to scale) shows the current model of presenting blood pressure targets, with different recommendations for diabetes, chronic kidney disease, and the elderly, though overlap between these conditions often occurs. (b) Suggested schematic for classification according to cardiovascular (cardiovascular) risk for blood pressure targets. Patients at high risk of adverse events (irrespective of cardiovascular risk) deserve individualized consideration for whom intensive targets may not apply.
Source: From Ruzicka et al. [56] used with permission. © 2017, Wolters Kluwer.

Advanced CKD

Little evidence exists about BP management in advanced CKD, once the GFR is less than 20 in particular, since these patients have been excluded from the large trials that guide practice. The outcomes of interest are indeed different in these patients, since the specter of dialysis looms much larger. Intensive BP lowering does cause a decrease in GFR, which in some patients might tip them over to dialysis.

Table 22.5 Details of the four major trials targeting BP thresholds in nondiabetic CKD.

Trial	Population	Outcomes: renal, CV and mortality
Klahr et al. (MDRD) [95]	$n = 840$ *Inclusion:* Age 18–70 years CrCl <70 ml/min MAP <125 mmHg *Exclusion:* Diabetes, Proteinuria >10 g/day Chronic medical conditions Body weight <80% or >160% standard body weight	*Decline in GFR* 10.7 (9.113.9) ml/min/3 years in usual BP arm 12.3 (10.6–14.0) ml/min/3 years in low BP arm *ESRD or death* RR 0.85 (0.60–1.22)
Wright et al. (AASK) [91]	$n = 1096$ *Inclusion:* Age 18–70 years GFR 20–65 ml/min *Exclusion:* Diabetes Clinical evidence of heart failure Proteinuria (urine PCR > 2.5 g/g) Serious systemic illness	*% risk reduction for GFR slope + ESRD* −2 (95% CI −31 to +20) *CV* 2.9% (lower BP) versus 3.4 % (usual BP) *Mortality* 1.6% (lower BP) vs. 1.9% (usual BP)
Rugenenti et al. (REIN-2) [96]	$n = 338$ *Inclusion:* Age 18–70 years Proteinuria 1–3 g/day and CrCl <45 ml/min OR Proteinuria >3 g/day and CrCl >70 ml/min *Exclusion:* Diabetes Overt heart failure (NYHA III or IV) Recent (<6 months) MI or CVA	*Decline in GFR* 0.22 ml/min/mo in intensified BP arm versus 0.24 ml/min/mo in usual BP arm ($P = 0.62$) *CV* 37 (22%) in intensified arm versus 25 (15%) in usual arm[a] *Mortality* 2 (1.2%) in intensified versus 3 (1.8%) in usual arm

(*Continued*)

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Table 22.5 (Continued)

Trial	Population	Outcomes: renal, CV and mortality
Wright et al. (SPRINT) [10, 94]	$n = 9361$ overall; 2646 with CKD *Inclusion:* Age >50 years AND • Clinical or subclinical CV disease OR • Framingham risk score > 15% OR • Age >75 OR • CKD (GFR 20–59 ml/min) *Exclusion:* GFR <20 ml/min Proteinuria >1 g/day (or albuminuria >600 mg/day) Residence in a nursing home, dementia Standing systolic BP <110 mmHg	*In CKD subgroup* *≥50% GFR reduction* RR 0.87 (0.36–2.07) *Dialysis* RR 0.57 (0.19–1.54) *CV* RR 0.82 (0.63–1.07) *Mortality* RR 0.73 (0.53, 1.00)

CVA, cerebrovascular accident; CV, cardiovascular disease; ESRD, end stage renal disease; GFR, glomerular filtration rate; MAP, mean arterial pressure; MI, myocardial infarction; NYHA, New York Heart Association; PCR, urine protein:creatinine ratio; RR, relative risk. Figures in parenthesis refer to 95% confidence intervals.
[a] Reported as "non-fatal serious adverse events, including myocardial infarction, congestive heart failure, stroke and cancer";
Source: Used with permission from Ruzicka et al. [56] © 2017, Wolters Kluwer.

Adverse effects from drugs required to lower BP, namely electrolyte disorders, are also more common in advanced CKD. This would specifically also apply to the use of RAS blockade. An ongoing trial in which 410 patients with progressive stage 4 or 5 CKD have been randomized to continue or stop ACEi/ARB will answer this question [105]. However, if the benefit of intensive BP lowering (i.e. a decrease in all-cause mortality and cardiovascular events) reported in the general population and milder stages of CKD applies to this population also, one has to consider this against the real risk of needing to start dialysis from worsening GFR. This trade-off requires shared decision making and open discussion about preferences and patient important outcomes. Additionally, initiation of dialysis should not be on the basis of GFR alone, which also might help some of the decision-making process [106].

Dialysis

The foremost question in dialysis populations is that of BP measurement. In hemodialysis (HD) though many BP measurements are taken during a session, many of those measurements do not necessarily provide a proper assessment of the overall BP load. Nevertheless, hypertension is very common in dialysis patients, with an estimated prevalence of 70–80% or higher, irrespective of whether predialysis BP or interdialytic measures using ABPM are used [107, 108].

Peritoneal Dialysis

BP measurement in peritoneal dialysis (PD) is less of a quagmire compared to HD, though we do not have any RCTs to guide us regarding the BP level which would best reduce CV outcomes and mortality in this population. Unlike some early estimates, hypertension is quite common in PD, and the overall prevalence is similar to that in HD [109]. High BP also has similar associations with CV outcomes, however, residual renal function and technique failure are additional important outcomes to consider. The circadian pattern of BP in PD is different than in HD which is not surprising given the nature of and timing of salt and fluid removal between the two modalities [110]. Given their benefit in preserving kidney function in nondialysis CKD, one should not be surprised that RAS blockade would be useful in this setting to preserve residual function as well [111]. Additional intriguing data suggests that spironolactone may be useful in this setting since it not only reduces BP, but increases potassium levels, which is useful since hypokalemia is quite common in PD patients [112]. With respect to volume management, body impedance analysis guided volume management resulted in a modest 2.7 mmHg drop in systolic BP with no impact on clinical outcomes [113]. The use of icodextrin-containing solutions is a useful method for better volume management and has been reported to lower BP in a few RCTs, without impairing residual function or having the deleterious effect of high glucose solutions [114, 115]. Reducing dialysate sodium to levels lower than what are commercially available is also an intriguing approach so far only tried in phase two trials [116, 117].

Hemodialysis

Which BP Measurement to Use?

Though predialysis and postdialysis BP measurements are considered most often, they are least useful given events around dialysis initiation, which may cause a physiological increase in BP. Interdialytic ABPM measurements, which can be done over the 44-hour interdialytic interval, provide a more accurate assessment of the BP load as well as the

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Subgroup	Studies	Baseline SBP	Events Intervention	Participants Intervention	Events Control	Participants Control	RR per 10 mmHg lower SBP	RR (95% CI)
Major Cardiovascular Events								
Diabetes	23	145	3999	30796	4007	28977		0.88 [0.82; 0.94]
No Diabetes	18	153	3494	52616	4035	46427		0.75 [0.70; 0.80]
Fixed effect model								0.81 [0.77; 0.85]
Test for interaction p=0.0006								
Coronary Heart Disease								
Diabetes	19	144	1404	26688	1487	25441		0.88 [0.80; 0.97]
No Diabetes	15	153	1143	41462	1389	35389		0.77 [0.70; 0.86]
Fixed effect model								0.83 [0.77; 0.89]
Test for interaction p=0.0627								
Stroke								
Diabetes	21	144	1263	29643	1368	28421		0.74 [0.65; 0.84]
No Diabetes	19	153	1691	52920	1978	46852		0.74 [0.67; 0.81]
Fixed effect model								0.74 [0.78; 0.80]
Test for interaction p=0.9533								
Heart Failure								
Diabetes	13	143	1028	21424	1094	20536		0.84 [0.72; 0.98]
No Diabetes	10	143	263	18578	373	18442		0.75 [0.65; 0.87]
Fixed effect model								0.79 [0.71; 0.88]
Test for interaction p=0.277								
Rental Failure								
Diabetes	9	143	760	14549	774	13641		0.88 [0.75; 1.03]
No Diabetes	4	146	592	9921	638	9952		0.92 [0.79; 1.07]
Fixed effect model								0.90 [0.81; 1.01]
Test for interaction p=0.7276								
All–cause Mortality								
Diabetes	20	144	2324	27562	2309	25782		0.87 [0.79; 0.97]
No Diabetes	17	153	1952	45588	2033	39414		0.83 [0.76; 0.90]
Fixed effect model								0.85 [0.79; 0.90]
Test for interaction p=0.4544								

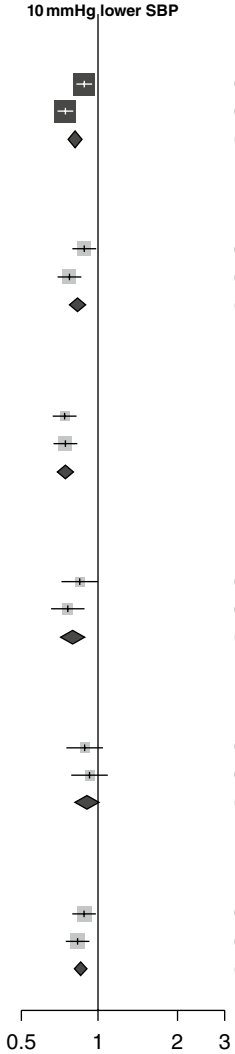

Figure 22.3 Standardized effect of a 10 mmHg reduction in systolic blood pressure (SBP) on the relative risk (RR) of major cardiovascular events, coronary heart disease, stroke, heart failure, renal failure, and all-cause mortality stratified by subgroups in which all (DM) or none (No DM) of the participants had diabetes mellitus at baseline. *Source:* From Ettehad et al. [4], used with permission. © 2016, Elsevier.

circadian pattern. Similar data exist about home BP, and these out-of-office measures are also more reproducible and have a stronger association with CV outcomes.

Early studies on BP and outcomes in hemodialysis reported a U-shaped curve of BP and survival in hemodialysis, and most concerning has been that the nadir of the U was reported at about systolic BP 160 mmHg, much higher than conventional thinking about BP targets and thresholds [118]. Although almost all other biological variables have a U-shaped relationship with clinical outcomes, the precise optimal BP being 160–180 mmHg would be a huge change from the ~120–140 in nondialysis populations. The former has indeed been reported, but those reports are from cross-sectional data and moreover rely on predialysis BP measurements. Cross-sectional data is notorious for susceptibility to selection bias and especially in HD populations is even more susceptible to reverse epidemiology [119]. Patients with heart failure, cancer, and patients in the last few months of their life have lower BP, and will also be more likely to die, independent of the BP. This leads to spurious associations which have been widely reported. In contrast, a meta-analysis of RCTs in dialysis patients shows a reduction of CV events with BP lowering [120]. Similarly, a linear relationship between BP and CV outcomes up to a systolic BP of 110–120 mmHg was reported when out-of-office BP measurement was used rather than predialysis BP [120, 121].

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Nonpharmacological Measures

Minimizing dietary sodium intake: The focus of communication with patients on dialysis is often on fluid intake, a thoroughly useless and futile waste of time and energy. Sodium intake drives fluid intake, and efforts to reduce sodium intake are likely to have a greater effect on BP in the dialysis population given the outsize contribution of sodium to BP in this population. Data supporting this is mostly from observational literature and, as before, the effectiveness of counseling on change in behavior is unknown.

Maximizing dialytic sodium removal: This can be achieved by adequate ultrafiltration by probing the dry weight, especially in patients with high BP even without any signs of overt volume overload, and by considering longer or more frequent dialysis in those who do not tolerate ultrafiltration. There is RCT-level evidence for the former as well as for the latter. These data, however, demonstrate efficacy in the form of a change in BP, but not on consequent clinical outcomes [122]. Longer and more frequent dialysis does not improve quality of life or longevity, and may have deleterious effects on vascular access and residual renal function, which are important considerations [123–126]. The last mechanism of maximizing sodium removal is by altering dialysis sodium. Observational data provide mixed evidence in this regard. The clinical trial data do suggest that lowering or individualizing dialysate sodium to patient serum sodium is an efficacious method of lowering BP [127–129] (see Table 22.6). Given the association of hemodynamic stability and lower cramps (both patient important outcomes) with higher dialysate sodium, higher quality data from an ongoing cluster RCT may help resolve this dilemma (Randomized Evaluation of Sodium Dialysate Levels on Vascular Events [RESOLVE] NCT 02823821).

Pharmacotherapy

From the limited trial evidence available, discussed below, the use of beta-blockers as initial agents, followed by RAS blockade and CCBs is a reasonable approach to be considered.

A few RCTs have been conducted of BP lowering drugs compared to placebo in HD patients. The results are decidedly mixed, owing potentially to small sample sizes, co-interventions, and open label designs. Two small RCTs suggest a benefit of beta-blocker use in improving survival. For RAS blockade, one RCT of fosinopril failed to show a benefit for CV outcomes ($P = 0.06$), and two small open label RCTs of different ARBs seemed to show a benefit on CV outcomes [130, 131]. The most rigorous of the RAS blockade trials is the most recent, which was open label, but had an adequate sample size and where the target BP was similar in both groups, and did not report any difference between the two arms for CV outcomes or for all-cause mortality [132]. Lastly, one RCT of amlodipine, which enrolled fewer patients and reported fewer events than expected, still reported a CV outcome benefit [133]. However, achieved systolic BP was about 10 mmHg lower in the amlodipine group, hence it is hard to separate the BP effect from the drug effect. Thus, to summarize, there are clear uncertainties about the benefits of these individual classes of drugs in HD patients. The existing data do seem sufficient to elevate beta-blockers, along with RAS blockade and CCBs, to the first line of therapy when needed to control BP. These data also suggest that BP lowering with pharmacotherapy overall is beneficial in decreasing CV events.

Some additional consideration is necessary to consider pharmacokinetic aspects, including the effect of dialyzability. Recent research has revealed that with modern high

Table 22.6 Clinical trials of changing dialytic sodium and blood pressure.

Study	Population	Design	Interventions	Results
De Paula et al. [127]	$n = 27$ Non diabetes and not prone to hypotension	Non randomized, prospective, crossover study 3 weeks each	Dialysate sodium 138 mmol/l or set to patients serum sodium	Individualized dialysate sodium decreased weight gain (− 0.6 kg) BP similar between two arms
Munoz Mendoza [128]	$n = 15$ In-center nocturnal hemodialysis	Prospective, crossover trial 12 weeks each (three phases)	Dialysate sodium 140 versus 136/134 versus 140	Lower dialysate sodium with lower weight gain (0.6 kg) BP change −8.3 mmHg (±14.9)
Inrig [158]	$n = 16$ Patients with history of intradialytic hypertension	Prospective, crossover trial 3 weeks each	Dialysate sodium set at serum sodium +5 or −5 mmol/l	Lower dialysate sodium lowered BP (mean −9.5 mmHg, 95% CI −13.4, −6.4 mmHg)

BP, blood pressure.

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flux dialysers, drugs such as bisoprolol, earlier thought to be nondialyzable, are indeed removed by dialysis [134]. On the other hand, despite atenolol being dialyzed out, it did show greater efficacy compared to lisinopril in one of the few RCTs in this area [135]. Thus it is not clear that dialyzability, or the lack thereof, matters in terms of efficacy in CV outcome reduction [136, 137]. However, the prolonged half-life of certain drugs can be used for more convenient dosing schedules, especially when there is a concern of nonadherence, and direct observed therapy can be provided with three times a week dosing in the dialysis unit [138].

An additional note is warranted about the utility of mineralocorticoid antagonists, namely spironolactone and eplerenone, which have had resurgence in resistant hypertension as well as in ESKD. Two trials suggest a fantastic benefit of these in lowering CV events and mortality, but both trials had a relatively small sample size to demonstrate such an outsize benefit [139, 140]. Another pilot/feasibility study of 100 patients did not demonstrate any difference, but did show a higher risk of hyperkalemia, borne out in a subsequent systematic review [141, 142]. Given these aspects, prudence would dictate awaiting the results of two large RCTs ongoing in this area (Aldosterone bloCkade for Health Improvement EValuation in End-stage Renal Disease [ACHIEVE] NCT03020303 and ALdosterone Antagonist Chronic HEModialysis Interventional Survival Trial [ALCHEMIST] NCT01848639).

Transplantation

In kidney transplant populations, additional contributors to hypertension include primarily the effect of immunosuppressive medications, but additionally the effect of the donor: recipient kidney volume mismatch, acute and chronic rejection, and transplant renal artery stenosis (often at anastomotic site) [143]. The steroid effect on BP is well known, and calcineurin inhibitors (CNIs) also increase BP by calcium channel mediated vasoconstriction, renal sodium retention, and in the long run by worsening kidney function. Specifically in the kidney transplant population, higher BP is associated with poorer patient survival, but also with more graft failure on the basis of observational data [144, 145].

With respect to treatment of hypertension, no trials have examined targets of BP lowering in these populations and guidelines have most often followed nontransplant CKD data. Given the role of immunosuppression, minimizing steroids and/or the CNI dose can assist in BP lowering, apart from the other nonpharmacological options discussed above. For specific pharmacotherapy, there do exist a few RCTs. The first line of agents, i.e. CCBs, RAS blockade, and even thiazide-like diuretics, are potent in lowering BP in this population [146, 147]. For outcomes, the strongest data support the use of CCBs as BP lowering drugs, as reported in this systematic review, and reduced graft loss (relative risk 0.75, 95% CI 0.57–0.99) [148]. For RAS blockade, the evidence is decidedly mixed when it comes to graft or patient survival. Overall, when combining ACE-inhibitors and ARBs as a class, there is no benefit seen against placebo or active comparators in this meta-analysis [149]. Intriguingly, the few ARB trials seem to report better graft survival than the ACEi RCTs, which may be a chance finding or worthy of further dissection or a larger replication [150, 151]. Other BP lowering drugs have little data on clinical outcomes and their use should be guided based on the BP lowering effect desired, adverse effects, and pharmacokinetics.

Guidelines and Variability

There is little agreement when it comes to the level of BP lowering in the plethora of existing international and national guidelines, even when it comes to the CKD subpopulation [152–154]. Despite a seeming overabundance of clinical trials, the same evidence is rated and weighed differently, resulting in this difference of opinion. Points that are common to all guidelines are that the systolic BP goal is <140 mmHg and the diastolic BP goal is <90 mmHg. The differences mostly arise with respect to how much lower should the BP target be and in whom should the BP be lowered further. Given that CKD itself is a robust risk factor for adverse CV outcomes, it would be sensible for intensive BP targets to be applied to this population. Previously mentioned caveats of identifying patients at high risk of adverse events and discussing risks and benefits and shared decision making, especially those of weighing outcomes which matter to the individual patients, do apply. The Kidney Disease Improving Global Outcomes (KDIGO) taskforce is also reviewing the data and will presumably come to a conclusion that may be acceptable to all in the coming months.

Research Needs

The discussion above highlights several lacunae in the evidence for management of hypertension in CKD patients.

- What are optimal BP targets in patients with diabetes and CKD?
- Is there a benefit with intensive BP lowering in patients with severe CKD (GFR < 20)?

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- What BP target should be used in PD patients? HD patients?
- Which outcomes are important for patients and what is the role of shared decision making for intensive BP lowering in CKD?
- What strategies can be used for improving adherence to BP lowering drugs?
- What are effective strategies for delivering nonpharmacological therapies for BP lowering?

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23

Renovascular Disease

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Introduction

End-stage renal disease requiring renal replacement therapy puts a major economic burden on the healthcare system. Atherosclerotic renovascular disease has been found in about 12–31% of patients >45 years old with end-stage renal disease [1, 2], constitutes the fastest-growing group of these patients [3], and is associated with a mean survival time of 25–34 months [4]. In unselected patients with hypertension, the prevalence of renal artery stenosis (RAS) is only about 1–5% [5]. In certain patient populations, such as those with severe hypertension, refractory hypertension, aortic aneurysm [6], or coronary artery disease [7], the prevalence is as high as 20–40% [8, 9].

Patients with RAS of >50–70% renal artery diameter were frequently advised to undergo correction of the stenosis. The reason for treatment usually was difficult-to-control hypertension. However, nowadays kidney failure should also be present, since patients with both hypertension and impaired renal function benefit the most from angioplasty. Identifying patients whose blood pressure and/or renal function will improve postintervention remains difficult. Retrospective studies have shown a lack of improvement in blood pressure and renal function despite correction of the stenosis in 20–46% of patients [10–16].

Because angioplasty and surgery can lead to complications like cholesterol embolism, persistent acute kidney failure, and even patient death, these procedures should only be performed in patients with a high likelihood of benefit. Possible reasons for a lack of treatment effect are correction of trivial stenoses (<60%), lack of a clinical problem (not difficult to control hypertension, not severely impaired or declining renal function) underlying renoparenchymatous disease, technical failure, cholesterol embolism, or radiocontrast toxicity. These aspects will be discussed.

Terminology

The term renovascular hypertension is reserved for those patients with improvement, or rarely even normalization, of blood pressure after intervention. The term renovascular azotemia is used for those patients who have improved renal function. Frequently, the term ischemic nephropathy is used, but this term does not distinguish whether a patient is going to be a responder. RAS and renovascular hypertension are frequently used as synonyms in the literature [17]. However, the term RAS should be reserved for an anatomical description, whereas renovascular hypertension and renovascular azotemia describe the functional relevance of the stenosis.

Pathophysiology of RAS

RAS leads to renal ischemia, causing the release of renin from the juxtaglomerular cells of the kidney and resulting in the conversion of angiotensin I to angiotensin II, subsequent release of aldosterone from the adrenal gland, vasoconstriction, and sodium and water retention. The long-term consequences are the buildup of extracellular matrix and collagen IV via angiotensin II-induced increased expression of transforming growth factor β and interstitial platelet-derived growth factor, resulting in irreversible parenchymal damage [18–20] also in the nonaffected kidney. The challenge of treatment of atherosclerotic RAS is to intervene at a stage before major parenchymal damage has occurred.

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Should we still Diagnose and Correct RAS?

At present there are 10 randomized controlled trials [15, 21–29] (Table 23.1), a metaanalysis [31], and a Cochrane analysis [30], none of which has shown a benefit of angioplasty compared to optimal medical treatment (OMT) alone. Some experts suggest we should stop looking for the presence of RAS because a benefit of correction of RAS has not been shown.

However, relevant patient groups have not been included in those studies. The second-largest ASTRAL trial [25] only included patients for whom the treating doctor was unsure whether angioplasty would be of help. The largest and most recent CORAL trial [27] included mostly patients without clinical problems (no severe hypertension, no declining renal function). Even if angioplasty were always futile – which it is not as will be shown – the diagnosis of RAS would still have to be made. All recent studies found a 50% less than expected event rate in the control group and attributed that to the OMT consisting of ASS, statins, and antihypertensives, including a RAS-inhibitor. Treating patients with OMT is class 1A advice in all guidelines and not looking for the presence of RAS would deny patients this treatment.

The Salford group included 72 patients in the ASTRAL trial and reported their outcome on a further 467 patients with >50% RAS who were not included in ASTRAL [33]. Thirty-seven patients had flash pulmonary edema but only 66% received angioplasty. The hazard ratio for death in the angioplasty group was 0.4 (0.2–0.9). Thirty-one patients had refractory hypertension and declining renal function. The hazard ratio for death in those patients receiving angioplasty was 0.15 (0.02–0.9) and the HR for a cardiovascular event was 0.23 (0.1–0.6). Vassallo et al. showed similar findings in 131 patients with ≥70% stenosis and clinical problems compared to 144 patients with the same degree of stenosis but without the clinical problem [34]. Median follow-up time was 58 months. Revascularitzation was associated with a 50% reduced risk of progression to end-stage kidney disease and cardiovascular events in patients with rapidly deteriorating renal function. Furthermore, patients with bilateral RAS and patients with proteinuria <1 g also had significantly better renal and cardiovascular outcomes post revascularization compared to controls.

Grey et al. reported findings on 39/207 patients with flash pulmonary edema or recurrent episodes of congestive heart failure. After angioplasty blood pressure and renal function improved significantly, and hospitalization for heart failure was reduced from 2.4 to 0.3 episodes per year before and after angioplasty [35].

This shows that correction of RAS may still be considered in patients with RAS and a relevant clinical problem.

A recent S2K guideline on diseases of the renal artery (https://www.awmf.org/uploads/tx_szleitlinien/004-008l_S2k_Erkrankungen-der-Nierenarterien_2020-01_01.pdf) describes case scenarios where angioplasty (usually stent assisted) should be avoided or can still be considered (Table 23.2) [32].

Patients who should be Screened for RAS

Because RAS is present in only about 1% of unselected patients with hypertension, general screening is not advisable. The clinical signs suggesting renovascular disease include an abdominal bruit, difficult-to-control hypertension (requiring three or more antihypertensive agents), accelerated hypertension or hypertension that was previously well-controlled, worsening of renal function 4–31 days after introduction of angiotensin converting enzyme inhibitor (ACEi) or angiontensin II receptor blocker treatment [10], severe atherosclerosis in other vascular beds, otherwise unexplained chronic kidney disease, hypertension associated with sudden and repeated left heart failure or pulmonary edema, the onset of hypertension before the age of 30 years in nonobese and 15 years in all patients (from fibromuscular renal artery disease) or after the age of 55 years (from atherosclerotic renal artery disease), and differences in the sizes of the two kidneys. It is important to identify these clinical clues because the prevalence of RAS increases to 39% among these patients [40]. Once RAS is suspected, a screening test is used to confirm its presence.

Screening Methods for RAS

Screening tests should be inexpensive, accurate (i.e. with a low rate of technical failure and high sensitivity and specificity), and noninvasive. This excludes angiography, although angiography is still considered the reference standard for detection and quantification of stenosis. A high interobserver variability for stenosis quantification has been shown ($\kappa < 0.4$) [41]. One study found a systolic pressure gradient of ≥30 mmHg in 13 of 22 renal arteries in which arteriography had shown only minor degrees of stenoses (<50%) [42], a pressure gradient generally associated with a reduction of the glomerular filtration rate (GFR) [43]. Angiography may also cause atheromatous embolization of the kidneys or renal impairment due to radiocontrast nephrotoxicity.

Spiral computed tomography angiography (CTA) and magnetic resonance angiography are noninvasive imaging

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Table 23.1 Randomized controlled trials angioplasty vs. no angioplasty.

Study	*n*	Inclusion	Exclusion	OMT	Follow up (months)	Blood pressure improvement	Antihypertensive drug classes	Renal function	Cardiovascular disease	SE-PTRA	Mortality
EMMA 1998 [21]	23/26	Stenosis ≥60–75%	Bilat. sten. Single kidney	No	6	Ø (24 h–RR)	−0.8 ($P = 0.009$)	Ø	NI	RR 3.4	Ø
Webster 1998 [22]	25/30	Stenosis >50%	RASi	No	6	Ø (office BP)	NI	NI	NI	↑	NI
DRASTIC 2000 [15]	56/50	Stenosis ≥ [30] 50%	Creatinine >2.3	No	3 12	Ø (office BP)	−1.0 ($P < 0.001$) −0.6 ($P = 0.10$)	Ø	NI	Ø	Ø
STAR 2009 [23]	64/74	Stenosis ≥ [30] 50%; GFR < 80 BP < 140/90	GFR < 15 PU > 3 g/Tag	Yes	24	Ø (office BP)	Ø	Ø	Ø	↑	Ø
NITER 2009 [24]	28/24	Stenosis >70% GFR 30-60		Yes	43	Ø (office BP)	Ø	Ø	Ø	↑	Ø
ASTRAL 2009 [25]	403/403	Stenosis >50% Doctor uncertain		Yes	33.6	Ø (office BP)	−0.22 ($P = 0.03$)	Ø	Ø	↑	Ø
RASCAD 2012 [26]	43/41	Stenosis: 50–80% KHK		Yes	12	Ø (office BP)	Ø	Ø	Ø (LVH)	Ø	Ø
CORAL [27]	459/472	Stenosis >80% oder >60% and PW > 20 mmHg syst	Creatinine >4 mg/dl	Yes + lifestyle	43	−2 mmHg syst ($P = 0.03$)	Ø	Ø	Ø		Ø
RADAR [28]	34/33	Stenosis >70%		Yes	36	Ø 24 h-RR	Ø	Ø			
METRAS [29]	~60	>70% oder <70% with poststenotic dilatation		Yes		?		Szinti			

n, number of angioplasty + OMT/OMT without angioplasty; Ø, no effect; OMT, optimal medical treatment (AHT (antihypertensive treatment) including RAS inhibitor, ASS, (Acetyl salicylic Acid) statin); NI, no information; GFR, glomerular filtration rate; PU, proteinuria; gray, primary endpoint; CVD, cardiovascular disease; SE- PTRA, side effect of angioplasty; PW, pressure wire.

Sources: Bavry et al. [31], Jenks et al. [30] and Oberhuber et al. [32].

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Table 23.2 Treatment of atherosclerotic renovascular disease [30–32].

Treatment	Recommendation	Certainty of evidence	Strength of recommendation
No angioplasty	No angioplasty in unilateral or bilateral asymptomatic stenosis	High	Medium [32]
No angioplasty	No angioplasty in patients with proteinuria >1 g/day, biopsy proven severe renal disease or resistive index >0.80	Moderate	Weak [32]
Angioplasty	Angioplasty can be considered in patients with both refractory hypertension and rapidly declining renal function (also with unilateral stenosis)	Low	Weak [32]
Angioplasty	Angioplasty can be considered in patients with flash pulmonary edema or recurring cardiac decompensation even in unilateral stenosis	Low	Medium [32, 35, 36]
Nicotin	Nicotine use must be stopped	High	Strong [32]
Statin	All patients with RAS should be treated with a statin to a goal of LDL < 70 mg/dl	Moderate	Medium [32, 37, 38]
Diet	Follow a healthy diet (salt restriction, moderation of alcohol consumption, high consumption of vegetables and fruits) and reduce weight and perform regular physical exercise	Moderate	Medium [32, 36]
Goal blood pressure	Blood pressure should be lowered to <140/90 mmHg	High	Strong [32]
RAS inhibitor	A RAS inhibitor should be given to all patients with unilateral RAS	Moderate	Medium [32, 39]
RAS inhibitor	A RAS inhibitor can be given to patients with bilateral RAS with tight control of s-creatinine and potassium	Low	Weak [32]
Aspirin	Acetylsalicylic Acid should be given	High	Strong [32, 36]
HbA1c	In patients with RAS and diabetes HbA1c should be ≤7.5%	Moderate	Medium [32]

techniques that have high sensitivity and specificity (>95%) for detecting RAS [44–47], although a more recent study did not find the same level of accuracy when these methods were applied in everyday practice [47]. The latter study reported a sensitivity of 64% and a specificity of 92% for CTA and 62% and 84%, respectively, for magnetic resonance angiography. These techniques are also limited by their high costs and, in the case of spiral CT, the use of contrast agents. Magnetic resonance is not suitable for patients with claustrophobia and certain types of metallic implants. Measurement of the concentrations of renin in the renal veins have been used to predict the potential success of surgical revascularization. False-negative and false-positive results are common with this technique, and it is therefore not recommended as a reliable screening test for RAS. In theory, the accuracy of renal vein renins is enhanced by using an ACEi (captopril test), which attenuates the vasoconstrictive effect of angiotensin II on the efferent arteriole and reduces filtration on the side of the stenosis [44]. The reported sensitivity and specificity after 25–50 mg of captopril, however, are also low [48].

Captopril scintigraphy (25–50 mg of oral captopril given 12 hours before isotope) can detect RAS with high sensitivity and acceptable specificity, and has also been shown to be of value in identifying patients whose blood pressure will improve after correcting the stenotic lesion [49]. This test, however, has not been shown to predict an improvement in renal function after correction of RAS and it cannot locate the stenosis or determine its severity [44]. Furthermore, the sensitivity of this test is reduced to 80% in patients with renal insufficiency (GFR of <50 ml/min) or in patients with bilateral stenoses or a stenosis in a single functioning kidney [44, 50]. It is particularly important to identify significant stenoses in these patients because the major rationale for performing surgery or angioplasty is to preserve renal function.

In experienced hands Doppler ultrasonography is highly sensitive and specific for detecting RAS, and it is rapid and inexpensive [51]. Two main approaches are used to detect a significant RAS of 50–70% [51]. The first (direct) approach looks at flow acceleration at the site of the stenosis. This approach has good sensitivity and specificity for detecting stenoses of ≥50%. Obesity, excessive bowel gas, or poor blood flow in the main renal artery can, however, interfere with direct visualization of the renal arteries [51]. The second (indirect) approach looks at poststenotic flow phenomena (tardus and parvus). This approach can be used in

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nearly all patients but will only detect severe stenoses of >60%. A combination of both approaches is the most suitable technique for accurate detection of RAS in almost all patients. In patients with normal or impaired renal function, we reported no technical failure with this combination method and showed high sensitivity (96.7%) and specificity (98.0%) for detecting RAS of ≥50% compared with angiography [51]. The value of Doppler ultrasonography to reliably detect stenoses of 50% and more has been shown in the majority of more recent studies (Table 23.3) and screening for RAS with Doppler ultrasound is favored by most guidelines [36].

In summary, the best screening test is probably the test performed most frequently at an individual facility. In patients with a GFR of <50 ml/min, CTA (due to radiocontrast toxicity) and captopril scintigraphy (due to low sensitivity) should be avoided.

Quantification of Stenosis and Estimation of Functional Relevance

Other than detecting the presence of stenosis, Doppler ultrasonography can also be used to estimate the severity of RAS with reliable estimates up to 70% diameter reduction. A good correlation compared to intravascular ultrasound has been shown ($R = 0.97$) [65]. An RI difference >0.05 (parvus phenomenon) suggests stenosis of at least 60% and an acceleration time >70 ms (tardus phenomenon) suggests a stenosis >65% [66].

There is general agreement [67] that a diameter stenosis of <50% causes neither high blood pressure nor impairment of renal function. For this reason, intervention should not be performed for these low-degree stenoses. Stenoses <60% progress slowly and almost never proceed directly to occlusion [68]. A policy of watchful waiting (e.g. ultrasonographic follow-up of stenoses) is reasonable. Stenoses of >65–80% are considered to be hemodynamically relevant [69, 70]. Stenoses in most studies have been graded by angiography. Simon et al. found hypersecretion of renin, suggesting functional relevance, in stenoses of >80% diameter reduction [70]. Unfortunately, data on the improvement of blood pressure or renal function after correction of stenosis are lacking. Giroux retrospectively evaluated the degree of stenosis in patients who did or did not have improved blood pressure after correction of RAS. They found tighter stenoses in patients that did benefit (79 ± 9% vs. 74 ± 9%, $P < 0.05$), but the differences were small [69]. Future studies should quantify stenoses using noninvasive Doppler ultrasound, intravascular ultrasound, or a pressure gradient measured by pressure wire (an expensive method) or catheter.

Exclusion of Renoparenchymatous Disease

Possibly the main reason for a lack of treatment benefit despite successful correction of RAS is preexisting renoparenchymatous disease. The two most frequent diseases coexisting with or even causing RAS are long-term hypertension and diabetes leading to hypertensive nephrosclerosis and diabetic glomerulosclerosis [71]. Renal biopsy can predict treatment failure but is usually not indicated in these disease entities [72]. Some readily available clinical and angiographic clues as predictors of treatment success have been suggested [73, 74] (Table 23.4). However, none of these parameters is sufficiently sensitive or specific, and contradicting data have been published for many of these. Rapidly deteriorating renal function in the presence of RAS has been associated with a favorable response after angioplasty [81]; however, follow-up data on renal function are frequently not available. Some screening methods have been evaluated regarding prediction of treatment success: measurement of renal vein renin, captopril scintigraphy, magnetic resonance tomography, and Doppler ultrasonography. Because a hemodynamically relevant RAS should cause increased renin production, renal vein renin measurements have been considered the reference standard for predicting the functional relevance of stenoses. The diagnostic accuracy of this test is, however, disappointing, and the requirement for invasive venous angiography and radiocontrast agents have made this method almost obsolete. Renal scintigraphy without captopril also has only low diagnostic accuracy, but captopril scintigraphy is an established method to predict a treatment effect. Captopril causes a further fall in GFR in the stenosed kidney. The positive predictive value for blood pressure improvement of a positive captopril scintigraphy is reported to be 92%; however, sensitivity drops to 80% in patients with impaired renal function [50]. This could be due to dependence of renal filtration on vasoconstriction of the efferent arteriole in patients with advanced renoparenchymatous disease, which is impaired after ACEi treatment. A further drawback of captopril scintigraphy is the requirement for meticulous patient preparation in order to obtain reliable results. Patient preparation includes controlled hydration, controlled sodium diet, and removal of diuretics and ACEi 4–14 days before the investigation [50, 82]. van Jaarsveld et al. did not find a predictive value of captopril scintigraphy for improvement of blood pressure in their study [15].

Gadolinium-assisted magnetic resonance imaging after ACEi treatment has been used to quantify renal filtration and has provided predictive results comparable to captopril scintigraphy [83]. The study protocol was later refined [84].

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Table 23.3 Stenosis criteria and sensitivity and specificity for detection of RAS with Doppler ultrasound compared to selective angiography[a].

Criterion and study [reference]	No. of patients	Criterion	% technical failure[b]	Degree (%) of stenosis[c]	% sensitivity/specificity
Direct stenosis criteria					
Hansen et al. 1990 [52]	74	RAR > 3.5	8	≥60	93/98
Karasch et al. 1993 [53]	53	V_{max} > 180 cm/s	15	≥50	92/92
Olin et al. 1995 [5]	102	V_{max} > 200 cm/s or RAR > 3.5	10	≥60	98/98
Postma et al. 1992 [54]	61	Doppler freq. >4 kHz and broadened Doppler spectrum	25	≥50	63/86
Schäberle et al. 1992 [55]	76	V_{max} > 140 cm/s	NA	≥50	86/83
AbuRahma et al. 2012 [56]	313	V_{max} > 285 cm/s	4	≥60	67/90
		RAR > 3.7			69/91
Indirect stenosis criteria (paravus, tardus)					
Baxter et al. 1996 [57]	73	AT > 70 ms	16	≥70	89/97
Kliewer et al. 1993 [58]	57	AT ≥ 70 ms	0	≥50	82/20
Riehl et al. 1997 [59]	214	RI < 0.45 or ΔRI ≥ 8%	0	≥70	93/96
Schwerk et al. 1994 [60]	72	ΔRI ≥ 5%	0	≥50	82/92
			0	≥60	100/94
Speckamp et al. 1995 [61]	123	ΔAI ≥ 80%	NA	≥70	100/94
Stavros et al. 1992 [62]	56	Loss of ESP	0	≥60	95/97
Strunk et al. 1995 [63]	50	AT ≥ 70 ms	4	≥50	77/46
Combination of direct and indirect stenosis criteria					
Krumme et al. 1996 [64]	135	V_{max} > 180 cm/s and/or ΔRI ≥ 5%	0	≥50	89/92
Radermacher et al. 2000 [51]	226	V_{max} > 180 cm/s and RRR > 4 and/or AT ≥ 70 ms	0	≥50	97/98

AI, acceleration index; AT, acceleration time; ESP, early systolic peak; RAR, renal aortic ratio; RI, resistance index (Pourcelot index); RRR, renal renal ratio.
[a] Only prospective studies with more than 50 patients and comparison with intra-arterial angiography as the gold standard were considered.
[b] Technical failure: the renal artery or intrarenal arteries could not be visualized by color Doppler ultrasonography.
[c] The lowest degree of stenosis (% diameter stenosis) detected by the respective ultrasound method. NA, data not available.

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Table 23.4 Predictors of a lack of effect of successful correction of RAS related to blood pressure and/or renal function.

	Studies [reference] that found the parameter to be:	
Patient characteristic	**Predictive**	**Not predictive**
Advanced age, >65 years	[15, 16, 75, 76]	[69, 77, 78]
Male gender	[75]	[69, 77, 78]
Severe atherosclerosis	[16, 69, 78]	
Proteinuria >1 g/day	[16, 79]	
Severely impaired renal function (GFR <40 ml/min)	[16, 78]	[69, 76, 77]
No sudden appearance of hypertension or sudden worsening of previously well-controlled hypertension	[15]	[16]
Duration of hypertension >10 years	[69, 75]	[76]
Diastolic blood pressure <80 mmHg	[69, 75, 76]	[77]
Systolic blood pressure <160 mmHg	[77]	[76]
Diabetes mellitus	[69]	[16, 78]
Nonsmoker	[16, 69]	
Degree of stenosis <70%	[69]	[15, 77]
Resistance index >0.80	[16]	[80]

Prospective studies on this fascinating technique as a predictor for renovascular hypertension or azotemia are lacking at present, however.

In two studies with low patient numbers, an increased intrarenal resistance index value measured by Doppler ultrasonography was associated with a rapid loss of renal function [85] and a lack of blood pressure improvement [86], despite correction of RAS. A prospective study found that a resistance index of >0.8 in the intrarenal segmental arteries had a sensitivity and specificity of >90% for predicting renal function deterioration and a lack of blood pressure improvement [16] (Figure 23.1).

Improving Short- and Long-term Results of Correction of RAS

Ten-year patency rates are still only available for surgically corrected renal artery stenoses, although outcomes may be better after surgery compared to angioplasty [87]. However, angioplasty has become the method of choice because it is less invasive and has a lower mortality rate. Only when an aortic aneurysm or other severe aortic disease requires simultaneous treatment should surgery be the preferred method. Ostial stenoses should always be treated with angioplasty plus stenting; stenoses located >1 cm distally to the aorta or stenoses due to fibromuscular dysplasia can be treated with angioplasty alone [88]. A randomized controlled study reported better initial patency rates (88% vs. 57%) and lower restenosis rates (14% vs. 48%) 6 months after stent-assisted angioplasty compared to angioplasty alone in ostial stenoses [89]. However, the same study failed to show superiority of stenting regarding blood pressure or renal function improvement. Newer studies report primary patency rates in the range from 94 to 100% [69, 77, 90], but long-term results are less favorable. Restenosis, de novo stenosis, or thrombosis rates in the range of 10% per year have been reported both in stent-treated patients and patients who had angioplasty alone [16, 69, 77, 81, 90–93] Revascularization success should therefore be monitored by ultrasonography at 3 months, 6 months, and yearly intervals thereafter. Newer technologies using sirolimus-coated stents are being evaluated [94].

Cholesterol Embolism and Radiocontrast Toxicity

Cholesterol embolism in the renal arterial bed or the aorta is always a dramatic event. It can lead to progressive loss of renal function despite patency of the renal artery. At present, there is no reliable method to detect cholesterol embolism. Renal biopsy is invasive and may miss the site of embolism due to sampling error. Blood eosinophilia, hypocomplementemia or the "blue toe" suggest cholesterol embolism but are not sufficiently sensitive or specific to allow the diagnosis of renal cholesterol embolism. Dejani et al. found blood eosinophilia of >5% in seven of 20 patients older than 55 years with impaired renal function (serum creatinine >2 mg/dl) treated by renal angioplasty [95]. The feasibility of renal protection devices catching cholesterol crystals and other debris has been shown but has not been tested in randomized controlled trials [96].

A further frequent complication associated with renal angiography and renal arterial stenting is radiocontrast toxicity. Treatment of RAS may be of greatest benefit in patients with impaired renal function, and these patients are most sensitive to radiocontrast toxicity. Controlled hydration with NaCl at 1 ml/kg/h for 12 hours prior to and after angioplasty is considered standard prophylactic therapy. A randomized controlled trial has shown the superiority of this regimen, compared with additional mannitol or furosemide treatment [97]. Prehydration with sodium bicarbonate (154 mmol plus 900 ml 5% glucose solution) instead of saline alone may further lessen the risk. However, these data have not been confirmed in subsequent studies [98]. Acetylcysteine (600–1200 mg twice a day) has been shown to have an additive

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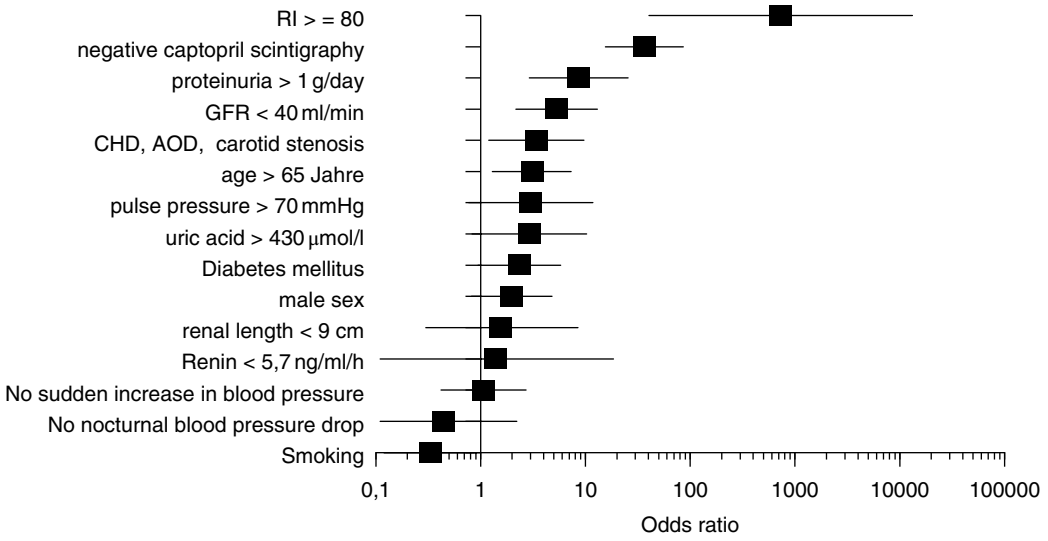

Figure 23.1 Odds ratios for various factors to predict deterioration of renal function. Squares depict odds ratios; lines depict 95% confidence intervals. RI, resistance index; CHD, coronary heart disease; AOD, atheroocclusive disease of the legs.

protective effect compared with hydration alone for preservation of renal function and prevention of acute kidney failure in several randomized controlled trials [99, 100], but a recent meta-analysis including 19 randomized trials failed to show such a protective effect [101].

The newer nonionic radiocontrast agents have lessened the risk of toxicity but have not abolished it [102]. Furthermore, the isoosmolar radiocontrast agent iodixanol has been associated with significantly less contrast nephropathy than the low-osmolar agent iohexol [103]. These results have not been confirmed in other studies. Hemodialysis during or directly after application of radiocontrast agents does not prevent radiocontrast toxicity, but hemofiltration may have a beneficial effect [104]. Here also, confirmatory studies have not been performed, and this method of treatment is invasive and expensive. Calcium channel blockers, ANP [105], dopamine [106], and endothelin receptor antagonist [107] have been proven useless to prevent radiocontrast toxicity. Theophylline may have a protective effect, but its effects are not additive compared to hydration treatment alone [108].

Conclusions

Patients should only be screened for the presence of RAS when the likelihood that they have RAS is sufficiently high. A good screening method is Doppler ultrasonography. If local experience favors CT or MRI these methods can also be applied. Only patients with a high likelihood for improvement should be treated with angioplasty. Randomized trials have failed to show a significant superiority of angioplasty compared to OMT alone. However, these studies included patients because they had anatomical RAS and not because they had RAS and a significant associated clinical problem. Future technical improvements regarding prevention of cholesterol embolism and radiocontrast toxicity may increase the proportion of patients who benefit from stenosis correction. Based on current data, stenoses of >60% can be treated with angioplasty if there is both uncontrolled hypertension and declining renal function, or if the patient suffers from flash pulmonary edema or recurring congestive heart failure.

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24

Secondary Diseases of the Kidney: Diabetic Nephropathy

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Diabetic Nephropathy vs. Diabetic Kidney Disease

Diabetic nephropathy classically refers to the renal microvascular pathology that occurs in patients with type 2 diabetes mellitus (DM) resulting in glomerular hyperfiltration, moderately increased urine protein, and severely increased urine protein, and followed by a reduction in glomerular filtration rate (GFR). It is generally accompanied by hypertension and other evidence of microvascular pathology, including retinopathy and neuropathy. It is characterized histologically by thickening of the glomerular and tubular basement membranes, mesangial expansion, and nodular sclerosis (Kimmelstiel–Wilson lesions). Although a recognized entity for 50 years [1], a pathological classification, dominantly based on glomerular pathology, has only been developed in the last decade [2] (Table 24.1). The classification also notes the presence of tubulointerstitial lesions, vascular lesions, and nondiabetic glomerular lesions which may be present to a variable degree in classic diabetic nephropathy [2] (Table 24.2).

It is now recognized that individuals, particularly those with type 2 DM and chronic kidney disease (CKD), do not uniformly present with the clinical features and trajectory of biochemical abnormalities outlined above, nor with the glomerular histological features listed in Table 24.1. Hence modern nomenclature has favored the term diabetic kidney disease (DKD) over diabetic nephropathy as this is more representative of the coexistent obesity-induced, vascular, and hypertensive kidney injury that is likely to be over-represented in patients with type 2 DM.

Incidence and Prevalence of Diabetic Kidney Disease

Diabetes is recognized as the world's fastest growing noncommunicable chronic disease. In 2003 the International Diabetes Federation (IDF) estimated that 194 million adults (aged 20–79 years) were living with diabetes and projected that this number would increase to 333 million people by 2025. However, in 2017 the IDF estimated 425 million people were living with diabetes and this number is expected to increase to 629 million by 2045 [3] (Figure 24.1).

In the 2017 report from the IDF [3], the highest prevalence is in China with 114 million people, followed by India with 73 million, and the USA with 30 million. The estimated worldwide expenditure on diabetes in 2017 was US $ 727 billion. Alarmingly, rates of childhood diabetes are increasing, being highest in the USA. Contrary to expectation, approximately one-third of the world population living with diabetes resides in nonurban environments and thus is arguably less likely to be strongly influenced by a Western diet. The vast majority of cases are due to type 2 DM, but the incidence of type 1 DM is also increasing, with a marked variation in the incidence and prevalence of type 1 DM across the globe that is currently unexplained.

The increasing prevalence of type 2 DM is driving the increased prevalence of kidney failure, with kidney failure 10 times more likely to occur in people with diabetes than in the remainder of the population [4]. The IDF estimate DKD is estimated to be responsible for between 12% and 55% of cases of kidney failure worldwide [3]. The proportion of kidney failure attributable to diabetes, hypertension, or a combination of

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Table 24.1 Glomerular classification of DKD.

Class	Description	Inclusion criteria
I	Mild or nonspecific LM changes and EM proven GBM thickening	Biopsy does not meet any of the criteria mentioned below for classes II, III, or IV
		GBM >395 nm in female and >430 nm in male individuals 9 years of age and older
IIa	Mild mesangial expansion**	Biopsy does not meet criteria for class III or IV
		Mild mesangial expansion in >25% of the observed mesangium
IIb	Severe mesangial expansion	Biopsy does not meet criteria for class III or IV
		Severe mesangial expansion in >25% of the observed mesangium
III	Nodular sclerosis (Kimmelstiel–Wilson lesion)	Biopsy does not meet criteria for class IV
		At least one convincing Kimmelstiel–Wilson lesion
IV	Advanced diabetic glomerulosclerosis	Global glomerular sclerosis in >50% of glomeruli
		Lesions from classes I through III

DKD: diabetic kidney disease
LM: light microscopy
EM: electron microscopy
GBM: glomerular baseline membrane
IFTA: interstitial fibrosis tubular atrophy
**The difference between mild and severe mesangial expansion is based on whether the expanded mesangial area is smaller or larger than the mean area of a capillary lumen
Source: Tervaert et al. [2]. © 2010, American Society of Nephrology.

Table 24.2 Interstitial and vascular lesions of DKD* [2].

Lesion	Criteria	Score
Interstitial lesions		
IFTA	No IFTA	0
	<25%	1
	25–50%	2
	>50%	3
Interstitial inflammation	Absent	0
	Infiltration only in relation to IFTA	1
	Infiltration in areas without IFTA	2
Vascular lesions		
Arteriolar hyalinosis	Absent	0
	At least one area of arteriolar hyalinosis	1
	More than one area of arteriolar hyalinosis	2
Presence of large vessels	–	Yes/no
Arteriosclerosis (score worst artery)	No intimal thickening	0
	Intimal thickening less than thickness of media	1
	Intimal thickening greater than thickness of media	2

DKD: diabetic kidney disease
IFTA: renal interstitial fibrosis and tubular atrophy
Source: Tervaert et al. [2]. © 2010, American Society of Nephrology.

both in the majority of countries where data are available is approximately 80%. As hypertension and diabetes are inextricably linked, ascertainment bias as to the cause of kidney failure may contribute to this variation. It is estimated that patients with CKD not requiring dialysis have 50% higher health costs compared to patients with diabetes but no CKD. In Australia, patients with CKD are 20 times more likely to die of a cardiovascular event than to reach kidney failure [5].

Pathogenesis of Diabetic Kidney Disease

The pathogenesis of DKD is complex, with multiple interacting and redundant pathways contributing to progressive kidney pathology. Mediators that are responsible for DKD (classically seen in younger patients with type 1 DM) overlap with additional factors more prevalent in patients with type 2 DM, including hypertension, macrovascular disease, and infection to result in a complex pathogenesis of kidney disease in patients with DM. With some significant exceptions, particularly regarding glycemic control, the majority of evidence to improve outcomes in DKD is based on trials in patients with type 2 DM and associated DKD.

Hyperglycemia is considered a key driver of DKD [6, 7]. It is directly or indirectly responsible for both metabolic abnormalities and altered intrarenal hemodynamics that contribute collectively to DKD. Intracellular hyperglycemia contributes to activation of the polyol pathway [8], hyperuricemia [9], dyslipidemia [10], the production of advanced glycation end products (AGEs), and interaction with receptors such as the receptor for advanced glycation end products (RAGE) leading to oxidative stress [11]. As a result, fibrosis, thrombosis, DNA damage, cellular dysfunction, vascular leakage, angiogenesis, inflammation, and decreased oxidative stress defense mechanisms are initiated, resulting in tubulointerstitial fibrosis [12, 13].

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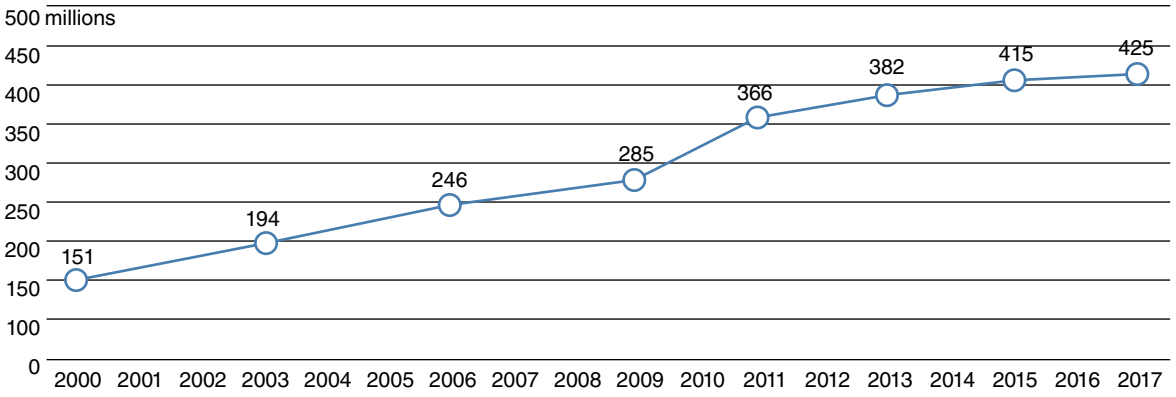

Figure 24.1 Estimates of the number of adults (aged 20–79 years) living with diabetes worldwide. *Source:* Based on Ogurtsova et al. [3].

Somewhat paradoxically DKD is associated with reduced mitochondrial superoxide production. A basal level of mitochondrial superoxide level is required to maintain adenosine monophosphate kinase (AMPK) activation and phosphorylation of endothelial nitric oxide to promote vascular dilatation under physiological circumstances. Reduced AMPK activity stimulates inflammatory transcription factors, including nuclear factor kappa B (NFκβ), and proinflammatory and profibrotic molecules in a paracrine manner from multiple renal cells. Under hyperglycemic conditions there is a reduction in mitochondrial superoxide generation, oxidative phosphorylation, and mitochondrial adenosine triphosphate (ATP) generation in the kidney and abnormalities in cellular bioenergetics occur [14, 15].

Vascular and glomerular lesions contribute to hypoxia, which further exacerbates oxidative stress in both the glomerulus and tubules [13, 16]. Hypoxia-inducible factors (HIFs) are induced with downstream transcription of genes such as vascular endothelial growth factor (VEGF) and erythropoietin to improve tissue oxygenation. However, there is experimental evidence that hyperglycemia may interfere with the stability of HIF and facilitate tissue fibrosis [17, 18].

These diverse mediators collectively lead to downstream activation of hormones and proinflammatory mediators [19] and profibrotic cascades. It is increasingly recognized that inflammation and fibrosis are inextricably linked in all forms of CKD, including DKD [20–23]. It is also now evident that as well as the adaptive immune system being activated in CKD, the innate immune system is also upregulated [24–28]. These responses are initiated by several classes of pattern recognition receptors (PRRs) in response to immune activators such as pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs). The latter are heterogenous molecules, derived from injured cells and components of the extracellular matrix (ECM), such as hyaluronan, biglycan, and fibronectin. DAMPs trigger innate immunity by activating Toll-like receptors, purinergic receptors, or the NLRP3 inflammasome, leading to necroptosis increased interferon gamma and downstream chemoattractants, macrophage chemoattractant protein-1 (MCP-1), and CCl10 [28–34]. Necroinflammation, an autoamplification loop between tubular cell death and interstitial inflammation, leads to the exacerbation of kidney injury [35, 36]. Although not yet specifically reported in DKD it is likely that common mechanisms are in play across the spectrum of CKD. Recent evidence suggests DAMPs also contribute to epithelial-mesenchymal transition of tubular cells to myofibroblast differentiation and proliferation. Furthermore, tubular cells also play an active role in progressive kidney injury via emerging mechanisms associated with a partial epithelial-mesenchymal transition and cell-cycle arrest at both G1/S and G2/M checkpoints [37].

It is clear that inflammation plays a major role in the pathogenesis of CKD. Inflammation occurs as a result of cellular injury, mediated by macrophages and lymphocytes [38–40]. The transcription factor nuclear factor kappa B (NF-κB) is responsible for upregulating genes involved in inflammatory processes within macrophages and tubular cells. Amplification of pro-inflammatory and pro-fibrotic cytokines, such as transforming growth factor β (TGF-β), platelet derived growth factor (PDGF), and fibroblast growth factor 2 (FGF-2), then occurs that causes migration and proliferation of resident fibroblasts. Such fibroblasts are differentiated, and along with tubular and glomerular cells ECM production is enhanced [41–43]. Resident and invading cells then secrete various chemokines, including MCP-1, IL-6, and tumor necrosis factor α (TNFα), that lead to further macrophage accumulation, perpetuating the development of fibrosis [44]. TGF-β, VEGFs, insulin-like

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growth factors (IGFs), and lipid mediators also contribute to inflammation and fibrosis [45].

As stated above, multiple transcription factors and cytokines are involved in expansion of the ECM, but TGFβ1 is considered the "master regulator" of kidney fibrosis in DKD. TGF-β1 is a well-characterized key mediator in the pathogenesis of tubulointerstitial fibrosis due to its direct and indirect effect on various cells types [46–49].

The direct action of TGF-β1 can initiate the transition of tubular and endothelial cells to a fibroblastic phenotype as described above and proliferation, migration, and synthesis of profibrotic proteins, such as collagens and fibronectin [50–56]. TGF-β1 can also induce an indirect fibrotic response via accelerating apoptosis of resident healthy cells and promoting resident and infiltrating cells to increase ECM deposition [57–59].

Hyperglycemia also causes release of vasoactive mediators, such as IGF-1, glucagon, nitric oxide (NO), VEGF, and prostaglandins, resulting in afferent arteriolar vasodilation. Additionally, both hyperglycaemia and insulin resistance result in dysregulation of the renin-angiotensin-aldosterone and endothelin [60] systems that act both systemically and specifically on the efferent arteriole. This results in peripheral and intraglomerular hypertension, leading to kidney impairment. [61]. Upregulation of proximal tubular sodium reabsorption occurs due to increased expression of sodium-glucose linked transport-2 and increased sodium-hydrogen exchange leading to a low sodium concentration at the macula densa and inhibition of tubuloglomerular feedback, thus resulting in single nephron glomerular hyperfiltration [62].

Shear stress as well as podocyte apoptosis driven by angiotensin II and endothelin, reduction in the slit diaphragm proteins nephrin and podocin, and glycation of the glomerular basement membrane with associated loss of negative charge results in albuminuria [63–65].

More recently, additional pathways have been identified as contributing to cellular dysfunction that predisposes to or accelerates the development of DKD. Both hyperglycemia and hyperinsulinemia trigger abnormalities in cell bioenergetics [66] that ultimately lead to inefficient use of metabolic substrates that contribute to tissue hypoxia. Additional dysregulated metabolic pathways, include upregulation of the mammalian target of rapamycin (mTOR), which drives suboptimal use of metabolic substrates, resulting in both cytosolic and mitochondrial derived dysregulated oxidative stress and dysfunctional autophagy and mitophagy [66–71].

Fatty acid beta-oxidation is the catabolic process by which fatty acid molecules are broken down in the cytosol and in the mitochondria to generate acetyl-CoA, which enters the citric acid cycle to produce ATP. The cellular mechanisms to ensure orchestrated fatty acid uptake, oxidation, and synthesis are tightly regulated to avoid excessive intracellular lipid accumulation. The transcription factors, peroxisome proliferator-activated receptors (PPARs), and PPARδ coactivator-1a (PGC1A) regulate the expression of proteins involved in fatty acid uptake and oxidation. In the setting of CKD lower expression of genes responsible for fatty acid oxidation, PPARs, and PGC1A is observed suggesting that lipid metabolism is impaired. Human proximal tubular studies have demonstrated that TGF-β is intrinsically involved in blocking fatty acid oxidation pathways, mediated by PGC1A [72].

Genetic and epigenetic modifications of both genes and histones induced by hyperglycemia, hypoxia, and as a consequence of proinflammatory and profibrotic pathways are increasingly recognized to influence the phenotype of individuals that directly or indirectly influences the development of diabetes and the propensity to develop DKD. Gene methylation or acetylation induced by hyperglycemia significantly influences the likelihood of gene expression or repression involved in the development of DKD. Similarly, hyperglycemia modifies the expression of noncoding mRNA including microRNA, long noncoding RNA, and small RNA, which collectively modify the expression of coding genes and therefore the phenotype of the individual with DM [73–80]. Increasingly it is recognized that epigenetic modifications, particularly of mitochondrial DNA, may be maternally transmitted from mother to offspring and hence predispose to population shifts in the propensity to chronic disease.

A schematic view of the key processes involved in the development of progressive kidney disease is summarized in Figure 24.2.

Screening and Diagnosis of Diabetic Kidney Disease

Moderately increased urine protein is an independent risk factor for the development of CKD and GFR loss [81, 82], as well as cardiovascular (CV) morbidities and mortality [83–86]. Most guidelines recommend annual screening for moderately increased urine protein in individuals with DM [87–90]. Screening should begin 5 years after the onset of type 1 DM and at the diagnosis of type 2 DM because of the inability to establish the onset of type 2 DM with certainty. Annual assessments of both albuminuria and of kidney function are commonly used screening tools [88]. Although a 24 hour urine collection was originally accepted as the gold standard for urinary albumin measurement, it is inconvenient to most patients and accuracy is flawed by inadequate

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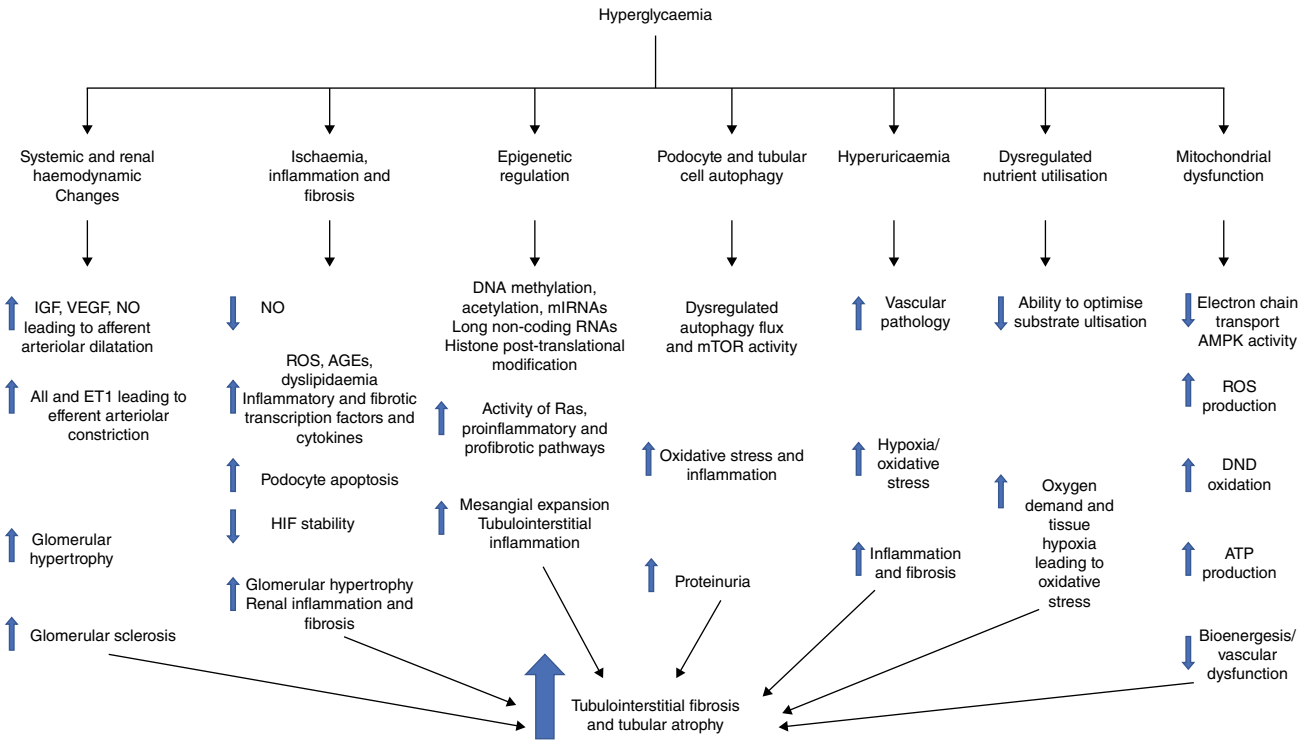

Figure 24.2 Schematic of the processes leading to tubulointerstitial fibrosis and tubular atrophy in DKD.
IGF: insulin-like growth factor
VEGF: vascular endothelial growth factor
NO: nitric oxide
ET1: endothelin-1
ROS: reactive oxygene species
AGEs: advanced glycation end products
miRNAs: microRNA
HIF: hypoxia inducible factor
ATP: adenosine triphosphate
DNA: deoxyribonucleic acid
RNA: ribonucleic acid

collection. Early-morning (or indeed random) urine assessment of the albumin-to-creatinine ratio (uACR) is now commonly used as a screening tool for the detection of DKD [88]. The random measurement of uACR has an inherent day-to-day variability (30–40%) [91], and may be elevated by factors independent of kidney disease, including strenuous exercise within 24 hours of measurement, urinary tract infection, menstruation, heart failure, marked hyperglycemia, and drugs, e.g. nonsteroidal anti-inflammatory drugs (NSAIDs). Therefore, an elevated uACR should be confirmed in the absence of urinary tract infection with two additional early-void specimens collected 3–6 months apart (Figure 24.3).

Although 24-hour collections are not commonly performed for the screening of DKD, they are useful when there is doubt about the accuracy of an estimated glomerular filtration rate (eGFR) (e.g. in populations where eGFR has not been validated such as where muscle mass is low) or when uACRs vary widely. Occasionally, 24-hour urine collections are also used

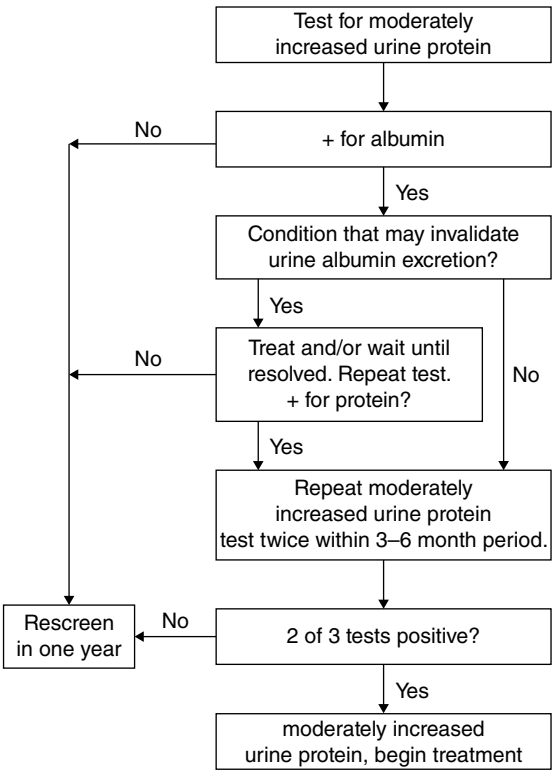

Figure 24.3 Screening for moderately increased urine protein recommended by American Diabetic Association (ADA) [89].

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to estimate daily dietary sodium and protein intake in individuals with DKD and refractory edema or hypertension.

The evidence for the utility of eGFR alone as a screening test for CKD in diabetes is unclear. The eGFR can be calculated using either the Modification of Diet in Renal Disease (MDRD) equation [92] or the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula [93]. Both equations perform well when the GFR is <60 ml/min/1.73 m^2 [92], but the CKD-EPI is more accurate at higher levels of kidney function [93]. Many patients with diabetes and classical "diabetic nephropathy" may have high-normal GFRs, particularly in the early stages of DKD. Therefore, progressive CKD is best determined by the slope of sequential eGFR measurements, rather than a single estimate. As alluded to above, other markers of kidney damage (e.g. albuminuria) are additionally required to detect early stages of CKD. The eGFR is useful for assessing progressive changes in kidney function but should not be used in situations where kidney function is changing rapidly, such as acute kidney injury (AKI) that can be observed in infection, hypotension or volume depletion.

Up to 52% of Japanese [94] and 55% of Australians [95] with type 2 DM had an eGFR of less than 60 ml/min and no evidence of moderately increased urine protein. In an Italian multicenter study 57% of patients with type 2 DM had an eGFR of less than 60 ml/min and normoalbuminuria, and had a significant risk of cardiovascular disease (CVD), although this was lower than if albuminuria and kidney impairment coexisted [96]. Porrini et al. have summarized the incidence of normoalbuminuric DKD to vary between 14% and 57% [97]. Hence CKD in patients with DM is likely to have multiple etiologies, including classical DKD. Despite this, an increase in urinary albumin, a decrease in eGFR or both in individuals with DM should reflect a diagnosis of DKD. In patients with DM, CKD should be attributed to diabetes if: i) severely increased proteinuria (previously known as macroalbuminuria) in the prescence of other microvascular complications ii) moderately increase proteinuria (previously known as microalbuminuria is present with either diabetic retinopathy, or in patients with type 1 DM of at least 10 years' duration. Other causes of CKD should be considered if any of the features listed in Table 24.3 is present. A kidney biopsy may be warranted in some cases for confirmation of diagnosis.

Table 24.3 Features indicative of a potential alternative diagnosis other than DKD.

- Absence of diabetic retinopathy
- Low or rapidly decreasing GFR
- Rapidly increasing proteinuria or nephrotic syndrome
- Refractory hypertension
- Presence of active urinary sediment, e.g. persistent microscopic hematuria
- Signs or symptoms of other systemic disease
- >30% reduction in GFR within 2–3 months after initiation of an ACE inhibitor or ARB

DKD: diabetic kidney disease
GFR: glomerular filtration rate
ACE: angiotensin-converting enzyme
ARB: angiotensin II receptor blockers

Prevention, Treatment, and Follow-up of Diabetic Kidney Disease

Lifestyle and Multifaceted Approach to Prevent and Treat DKD

Lifestyle interventions such as reduced salt intake, weight loss, physical exercise, and supplementation with polyunsaturated fats have been shown to improve glycemic control, lower blood pressure (BP), reduce albuminuria, and change metabolic risk profiles in the general population as well as in individuals with diabetes and CKD [98–101]. However, there is no evidence that lifestyle modifications reduce the risk of DKD or slow its progression. Dietary sodium restriction has been shown to reduce BP and albuminuria, and enhance the response to RAAS inhibition [102–104]. However, optimal dietary sodium intake in DKD remains controversial, with observational studies showing a benefit [105] or conversely a detrimental effect on wellbeing and mortality [104, 106, 107]. In reality, multiple risk factors are managed concurrently in patients with diabetes and kidney disease. In the STENO study, 80 Danish patients of European descent with type 2 DM and moderately increased urine protein were randomly assigned to receive conventional treatment in accordance with national guidelines and another 80 to receive intensive treatment, with a stepwise implementation of behavior modification and pharmacologic therapy that targeted hyperglycemia, hypertension (RAAS blockade), dyslipidemia, and moderately increased urine protein, along with secondary prevention of CVD with aspirin. The outcomes were first reported in 2003 with a mean follow-up of 7.8 years [108, 109]. Patients receiving intensive therapy had a significantly lower risk of CVD (hazard ratio [HR] 0.47, 95% confidence interval [CI] 0.24–0.73), nephropathy (HR 0.39, 95% CI 0.17–0.87), retinopathy (HR 0.42, 95% CI 0.21–0.86), and autonomic neuropathy (HR 0.37, 95% CI 0.18–0.79) compared to those receiving a standard approach. Patients in the intensive arm showed a mean decrease in albuminuria and lower incidence of progression from moderately to severely increased urine protein (but not for the development of kidney failure) [109] and a reduction in the composite outcome of CVD events or death by about 50% when compared to the group treated

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with standard therapy. After 7.8 years, the study continued as an observational follow-up with all patients receiving treatment as for the original intensive-therapy group, and recently reported a 21.2 years follow-up ($n = 22$ conventional group, $n = 42$ intensive group) that shows a median of 7.9 years of gain of life mainly driven by time free from incident CVD [110]. Median time before first CV event after randomization was 8.1 years longer in the intensive-therapy group ($P = 0.001$). Microvascular complications were study predefined tertiary endpoints. Progression of retinopathy was decreased by 33%, autonomic neuropathy was decreased by 41%, and progression to diabetic nephropathy (severely increased urine protein) was reduced by 48% in the intensive-therapy group when compared to the conventional groups. Ten patients in the conventional-therapy groups versus five patients in the intensive-therapy group progressed to kidney failure ($P = 0.061$). The nonfatal endpoints and causes of death were adjudicated by an external endpoint committee blinded for treatment allocation.

The Look AHEAD (Action for Health in Diabetes) multicentre trial is the largest randomized trial to date evaluating the efficacy of a physical activity and dietary control intervention (targeting a ≥7% weight loss) in older obese adults with type 2 DM. The study randomly assigned 5145 obese participants with type 2 DM to either intensive lifestyle intervention ($n = 2570$) or standard diabetes support and education ($n = 2575$). Intensive lifestyle intervention was designed to achieve and maintain weight loss through reduced caloric consumption and increased physical activity (a minimum of 175 min/week of unsupervised exercise). Major CV event rates were not significantly different in the two groups, which resulted in early termination of the study. After a median of 8.0 years of follow-up, the study demonstrated slower progression of CKD in the intensive lifestyle intervention group than patients in the comparator group. The incident CKD rate was 0.91 cases per 100 person-years in the standard group and 0.63 per 100 person-years in the intensive lifestyle group (difference 0.27 cases per 100 person-years, HR 0.69, 95% CI 0.55–0.87, $P = 0.0016$) [111]. The Intensive lifestyle intervention group achieved significantly greater and more sustained improvements secondary outcomes, including weight loss, improved cardiorespiratory fitness, improved glycemic control, BP, and lipids with fewer medications, as well as decreased rate of sleep apnea, retinopathy, depression, sexual dysfunction, urinary incontinence, and knee pain, plus better physical mobility maintenance and quality of life, with lower overall healthcare costs. There were no safety signals suggestive of kidney-related adverse events.

These studies are limited by the difficulty in attributing which facets of the intervention are associated with reduced risk. Despite the low-level evidence that studies using a multipronged approach to risk-factor management provide, the importance of addressing multiple risk factors needs to be considered for renoprotection but also for benefits on mortality and cardiovascular events, which are more likely to occur in patients with DKD than is kidney failure [112–114]. The Kidney Disease Improving Global Outcomes (KDIGO) Guideline 2020 [115] recommended moderately intensity exercise in people with diabetes and CKD. Recently, a new study by Cohen et al [116] compared bariatric surgery (laparoscopic surgery) versus standard care (non-surgery intervention) in 100 patients with type 2 DM and CKD stages G1-G3, during a follow-up of 2 years. The study reported zero events for mortality (both all-cause and cardiovascular) and no cardiovascular events. However, bariatric surgery improved remission of albuminuria (<30 mg/g) in participants who received bariatric surgery compared to standard of care (Relative risk (RR) 1.44 , 95%CI 1.03, 2.02).

Glycemic Control

Tight sugar control is critical, and hyperglycemia can cause organ complications. Therefore, optimal glycemic control is integral to the management of DKD. Regardless of the underlying treatment, glycated hemoglobin HbA1c: glycated haemoglobin levels >7.0% (53 mmol/mol) are associated with a significantly increased risk of both microvascular and CV complications [7, 117,118]. These studies show a curvilinear relationship between HbA1c and diabetes complications, with no apparent threshold of benefit, although the absolute reduction in risk was much at lower HbA1c levels. Most of the evidence comes from studies of intensive glycemic control in people with type 1 and 2 DM and early CKD. The evidence for the risks and benefits of intensive glycemic control is scant for more advanced stages of CKD, including individuals receiving dialysis or kidney transplant recipients.

The Diabetes Control and Complications Trial (DCCT) in type 1 DM [6], the Kumamoto trial [119], and the United Kingdom Prospective Diabetes Study (UKPDS) [117,120] in patients with type 2 DM confirmed that improved glycemic control significantly reduced the risk of microvascular complications, but had no significant effect on CV outcomes. Subsequent observational long-term follow-up after termination of both the DCCT and UKPDS studies showed a persistence of significant microvascular benefits and also demonstrated the emergence of a beneficial effect on CV outcomes attributed to intensive glycemic control. In the DCCT cohort, there was a significant reduction in CV outcomes (42%), nonfatal myocardial infarct (MI), stroke, and CV death (57%) as well as all-cause mortality (33%) in previously intensively treated participants compared with those who were previously in the standard arm [121–123]. Similarly, there was a significant reduction in MI (15–33%) and all-cause mortality (13–27%) in the UKPDS cohort in participants who

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had been originally randomized to intensive treatment [124].

The Action to Control Cardiovascular Risk in Diabetes (ACCORD), Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE), and Veterans Affairs Diabetes Trial (VADT) are three major trials that examined the effect of intensive glycemic control on people with long-standing type 2 DM. The ACCORD trial randomly assigned 10 251 participants with type 2 DM who had either an established CVD history or multiple risk factors for CVD to intensive therapy targeting an HbA1c <6.0% (42.1 mmol/mol) or standard therapy targeting an HbA1c level of 7.0–7.9% (53–62.8 mmol/mol) [125]. The mean age of participants was 62 years and the mean duration of diabetes was 10 years. A difference in HbA1c was rapidly obtained and maintained throughout the trial at 6.4% (46.4 mmol/mol) and 7.5% (58.5 mmol/mol) in the intensive and standard therapy groups, respectively. The primary composite major CV outcomes (nonfatal MI, nonfatal stroke, or death from CV causes) were not different between two arms (HR 0.90, $P = 0.16$). The glycemic control portion of the trial was prematurely terminated after 3.5 years due to higher mortality in the intensively treated arm. Intensive glycemic control arm showed a 32% reduction in the development of incident of severely increased urine protein (2.7% vs. 3.9%) and a 21% reduction in the development of incident of moderately increased urine protein (12.5% vs. 15.3%) [125, 126]. However, an observational follow-up of the surviving participants in the ACCORDION study ($n = 8601$) over a median of 8.8 years showed a neutral long-term effect of intensive glucose control on the composite CV outcome and all-cause mortality (HR 1.01, CI 0.92–1.10) [127]. In the same follow-up study, intensive glycemic control significantly reduced the development of severely increased urine protein (HR 0.68, CI 0.59–0.77) but had no impact on doubling of serum creatinine or need of dialysis [128].

The ADVANCE study was a 2×2 factorial designed randomized control trial randomly assigning 11 140 participants to standard (targeting HbA1c based on local guidelines) or intensive glucose control therapy aimed at reducing HbA1c to ≤6.5% (47.5 mmol/mol) [23]. Participants were ≥55 years of age with a history of major CV or microvascular disease or at least one other risk factor for CVD. The mean duration of diabetes was 8 years. After a 5-year follow-up, the mean achieved HbA1c was 6.5% (47.5%) in the intensive group and 7.3% (56.3 mmol/mol) in the standard group. The primary outcome was a composite of microvascular events (nephropathy and retinopathy) and CV disease defined by major adverse CV events. There was a significant reduction in the incidence of major microvascular events in the intensive arm, largely driven by a 21% relative reduction in nephropathy, including new or worsening nephropathy and kidney failure. The number of participants needed to treat over 5 years to prevent one kidney failure event ranged from 410 in the overall study to 41 participants with severely increased urine protein at baseline. Thus, improved glucose control improved major kidney outcomes in patients with type 2 DM [129]. However, the small number of kidney failure events observed during the trial limited the strength of the conclusion [129]. There was no reduction in major CV events or all-cause mortality in the intensive glucose lowering either during the in-trial period or observational follow-up of a median 5.4 years [130]. In the post-trial observational follow-up ADVANCE-ON study, there was a significant reduction in the risk of kidney failure with intensive glucose lowering that was observed during the in-trial period (7 vs. 20 events, HR 0.35, 95% CI 0.15–0.83, $P = 0.02$) that persisted after a total of 9.9 years of follow-up (29 vs. 53, HR 0.54, 95% CI 0.34–0.85, $P < 0.01$) [129, 130]. The patients who appear to benefit most from intensive glycemic control are those with preserved kidney function (early stages of CKD) and those with better blood pressure control at baseline (systolic BP <140 mmHg). This also shows that CKD stages at baseline did not affect the impact of intensive glucose lowering on mortality or major cardiovascular events [131].

Neither study demonstrated a reduction in CV events or mortality with intensive glycemic control. This raises the question of whether optimal HbA1c may differ for microvascular/renoprotection versus cardiovascular events. In addition, the safety of intensive glucose control in the presence of CKD has been questioned, with the ACCORD trial [132] reporting that its intensive glucose lowering strategy increased the risk of cardiovascular and all-cause death among participants with CKD, but not in those with normal kidney function.

A smaller VADT study randomly assigned 1791 United States military veterans with a mean duration of diabetes of 12 years and poor glycemic control (≥7.5% or 58.5 mmol/l) to either standard or intensive glucose lowering therapy, which aimed for an overall reduction in HbA1c levels by 1.5% [133]. The mean duration of diabetes was 12 years and the HbA1c levels achieved in the intensive and standard therapy groups were 6.9% (51.9 mmol/mol) and 8.4% (68.3 mmol/mol), respectively. During a median follow-up of 5.6 years, there was a nonsignificant reduction in the primary outcome (first occurrence of a major CV event), but the progression to albuminuria was significantly reduced in the intensive-treated group 17% vs. 35% standard-treated group after 2 years ($P = 0.05$). During an observational median follow-up of 9.8 years, the intensive-treated group had a significantly lower risk of the primary outcome (MI, stroke, new or worsening congestive heart failure [CHF], amputation for ischemic gangrene, or CV-related death) than did the standard therapy group (HR 0.83, $P = 0.04$), with an absolute reduction in risk of 8.6 major CV events

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per 1000 person-years [134]. There were no differences in kidney failure between groups in the VADT [133] or VADT-F [134], its long-term follow-up study.

Data from a meta-analysis from 58 160 patients in 13 randomized controlled trials suggest that people with type 2 DM who receive intensive glucose-lowering therapy have a reduced risk of the composite major adverse cardiovascular events (MACE) and MI, with no significant effect on the risk of total mortality, cardiac death, stroke, and CHF [135]. A further meta-analysis examined intensive versus standard glycemic control in 27 391 adult patiants with type 2 DM and CKD from four randomized controlled trials (RCTs) and found the pooled odds ratio (OR) for the doubling of serum creatinine and need of dialysis were not statistically significant, i.e. 0.98, 95% CI 0.81–1.19, and 0.84, 95% CI 0.69–1.02, respectively. The pooled OR for the outcome of death from kidney failure was 0.62, 95% CI 0.39–0.98 [136].

Hypoglycemia is more common as lower HbA1c levels are targeted, and people with CKD are at an increased risk of hypoglycemia [137, 138]. In the ACCORD study, hypoglycemia in the intensively treated group was associated with an increase in mortality [125]. The frequency of severe hypoglycemia in these trials was two to three times higher in the intensive therapy groups and a higher mortality was reported in participants with one or more episodes of severe hypoglycemia in the ACCORD [30], ADVANCE [31], and VADT trials [25], irrespective of the different treatment arms in which individual participants were allocated. Therefore, it has been suggested that tight glycemic control with a target HbA1c of 6.0% may not be ideal for older/frail individuals or those with longer duration of diabetes, advanced coronary artery disease (CAD), and a known history of severe hypoglycemia. It also highlights individualized glycemic control targeting, with patient education, and monitoring for hypoglycemic episodes should be an important component of management plans in patients with DKD.

Monitoring of glycemic control in DKD can be problematic. HbA1c is most commonly used but is influenced by shortened red blood cells (RBCs) survival in patients with DKD in the uremic millieu [139, 140], use of erythropoietin, carbamylation of hemoglobin [141], and mechanical destruction of RBCs on dialysis. Thus, clinicians may often need to rely more on random or continuous home blood glucose monitoring, which raises practical and cost challenges. Alternatives to HbA1c such as fructosamine, glycated albumin, and 1,5-anhydroglucitol (1,5-AG) have been proposed. These biomarkers have been shown to reflect glycemic control in CKD and also post-prandial glucose fluctuations. Serum 1,5-AG may be useful for estimating within-day glucose variations. However, each has its inherent limitations [142] and no relationship to the development or limiting the progression of DKD has been demonstrated. Evidence from adequately powered clinical trials is required to determine whether any of these monitoring tools provide superior to HbA1c in patients with DKD.

Pharmacotherapy for Glucose Lowering in DKD

Slowing the progression of DKD has been the subject of both primary and secondary endpoints in studies of patients with DM. Initial studies were primarily targeted to lower blood glucose and/or blood pressure. Subsequently, specific studies were undertaken to assess the benefit of interrupting the renin angiotensin system in patients with DKD, with or without tight glycemic control. Collectively these studies have established that current best practice includes interruption of the renin angiotensin system to slow progression of kidney disease [143, 144].

The requirement of the Food and Drug Administration (FDA) to undertake cardiovascular endpoints in drugs being brought to market for glycemic control has increased our knowledge of potential kidney benefits in the diabetic population when specific interventions are used to improve glycemic control. Although currently available data reflect secondary endpoints, studies adequately powered to demonstrate kidney benefits of agents primarily developed for glycemic control are underway. More recently therapies have been trialed to interrupt specific pathways considered to be of key importance in the development of DKD.

Sodium-Glucose Linked Co-transport-2 Inhibitors

The combined sodium-glucose linked co-transport-1 and -2 (SGLT1 and 2) inhibitor phlorizin was initially isolated from the bark of apple trees in 1835. It was recognized soon after that the compound caused glycosuria, polyuria, and weight loss. However, interest in inhibiting tubular reabsorption of glucose as a potential treatment for DM did not emerge till the 1970s with discovery of the location of SGLT transporters in the kidney. Phlorizin was not pursued as a treatment for hyperglycemia due to poor oral absorption and concurrent blockade of SGLT1, resulting in diarrhea and gastrointestinal side effects due to inhibition of intestinal glucose and galactose absorption. As SGLT2 is responsible for more than 90% of glucose reabsorption in the proximal tubule of the kidney, specific SGLT2 inhibitors were developed. Clinical trials initially focused on the efficacy of glycemic control in patients with type 2 DM. Given the glucose-lowering effects are dependent on glomerular filtration delivering glucose to the tubular lumen, where the SGLT2 transporters are situated, initial studies did not include patients with more than mild degrees of kidney impairment. Two

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large cardiovascular (CV) endpoint trials have been reported to date in patients with type 2 DM at high risk for future cardiovascular events. Both the EMPA-REG [145] and CANVAS/CANVAS R trials [146] showed an impressive reduction in important cardiovascular endpoints, but importantly secondary analyses of kidney endpoints in both studies showed a significant and remarkably similar benefit on kidney-specific outcomes in this high-risk population. Specifically, of the 7020 patients studied in EMPA-Reg, approximately 1800 had eGFR <45 ml/min, 750 had severely increased urine protein, and 80% were on renin-angiotensin system blockers. Overall the study demonstrated a 39% reduction in new-onset or worsening of existing nephropathy (HR 0.61, 95%CI 0.53–0.7), a 46% reduction in the composite outcome of doubling of serum creatinine, initiation of kidney replacement therapy, and death due to kidney disease in the empagliflozin group (HR 0.61, 95% CI 0.53–0.7). The impact of empagliflozin on the primary endpoint was not diminished in patients with CKD compared to those without it (MACE HR 0.88, CV death HR 0.78, heart failure HR 0.59, all-cause mortality HR 0.80, no signal of MI, stroke) [147].

Similarly, in the CANVAS study the composite outcome of sustained doubling of serum creatinine, kidney failure, and death from kidney causes occurred less frequently in the canagliflozin group compared with the placebo group (HR 0.53, 95% CI 0.33–0.84), with consistent findings across prespecified patient subgroups. Annual eGFR decline was slower (slope difference between groups 1·2 ml/min/1.73 m^2 per year, 95% CI 1.0–1.4) and mean uACR was 18% lower (95% CI 16–20) in participants treated with canagliflozin than in those treated with placebo [148].

The DECLARE-TIMI58 study compared dapagliflozin with placebo in >17 000 individuals with type 2 DM and variable risk for CVD. The outcomes were reported in a scientific session at the American Heart Association (AHA) meeting in November 2018 and indicate that dapagliflozin is noninferior but not superior for reducing MACE in patients with this cohort. The composite rate of cardiovascular death or hospitalization for heart failure was 17% lower for patients receiving dapagliflozin compared with those who received placebo (4.9% vs. 5.8%). Kidney events and predefined composite outcomes (defined as new kidney failure, eGFR decrease by at least 40% to less than 60 m/min/1.73 m^2, or death from kidney or CVD) were 23% lower in the dapagliflozin group (4.3% vs. 5.6%, $P < 0.05$, compared to placebo) [149].

The mechanism of action benefit for this class of drug for both cardiac and kidney outcomes has been widely discussed and potential mechanisms are detailed in Figure 24.4.

Clearly these results are derived from secondary endpoints of studies primarily powered to determine CV outcomes. The CREDENCE study was designed to determine the efficacy and safety of canagliflozin versus placebo at preventing clinically important kidney and cardiovascular outcomes in patients with diabetes and established kidney disease [151]. CREDENCE randomized 4401 adults with type 2 DM, eGFR ≥30 to <90 ml/min/1.73 m^2, and severely increased urine

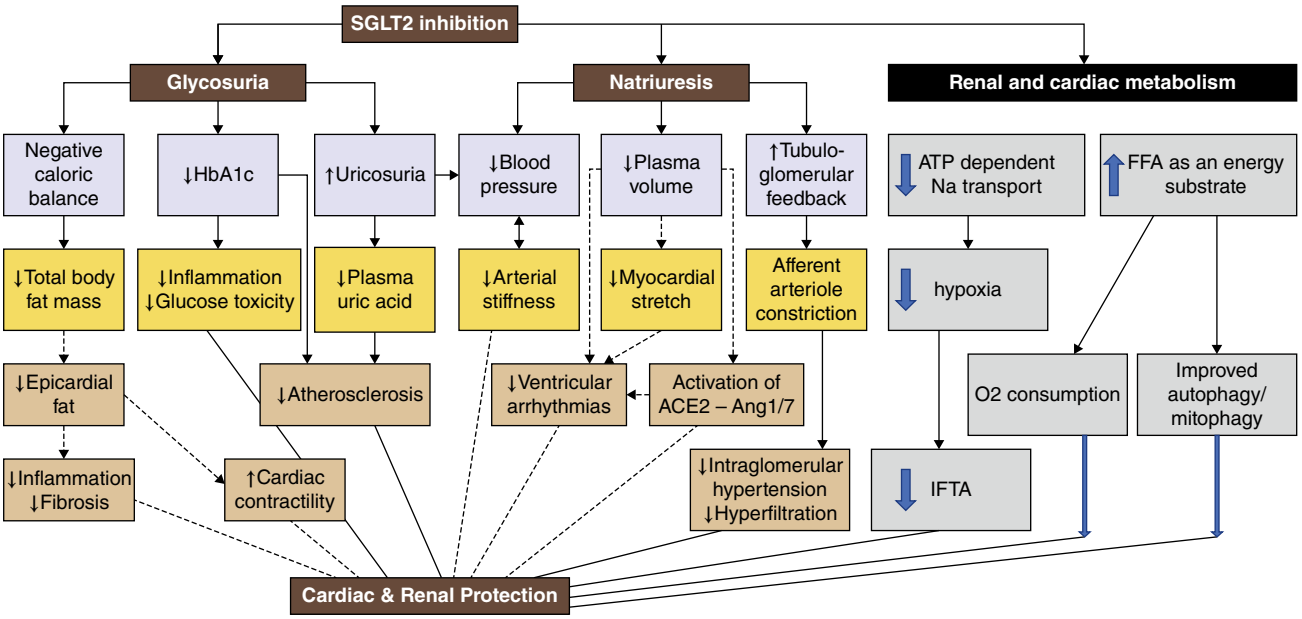

Figure 24.4 Proposed mechanisms of benefit for cardiovascular and kidney outcomes with the use of SGLT2 inhibitors. *Source:* Adapted from Rajasekeran et al. [150].

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protein (uACR >300 to ≤5000 mg/g) with a median follow-up of 2.62 years. The CREDENCE study was terminated early on the advice of the Data Safety Monitoring Committee because of the magnitude of efficacy in the intervention arm, which found a 30% lower risk of the primary composite endpoint is kidney failure, doubling of serum creatinine, and kidney or CV death in the canagliflozin arm compared to standard of care (HR 0.70, 95% CI 0.59, 0.82) [151].

Because the mechanism of benefit of SGLT2 inhibitors appears to be somewhat independent of glycemic control, several studies have been developed and undertaken to assess whether these drugs have renoprotective benefits in patients with type 1 DM and in patients with non-DKD. DAPA-CKD study [152], compared dapagliglozin 10 mg with placebo in 4304 participants with CKD with or without diabetes. The study found a decrease in the primary composite outcome of sustained decline in eGFR at least 50%, kidney failure, kidney-related or CV mortality in both participants with type 2 DM (HR 0.64, 95% CI 0.52,0.79) and those without diabetes (HR 0.50, 95% CI 0.35, 0.72). Further studies are also planned in the CKD population without diabetes (EMPA- Kidney, http://ClinicalTrials.gov, Identifier NCT03594110). A Cochrane systematic review which is undergoing an update [153] reported that SGLT2 inhibitors decrease all-cause mortality (17 studies, 31523 participants; HR 0.88, 95% CI 0.82 to 0.95; $I^2 = 0\%$, *high certainty evidence*), cardiovascular mortality (12 studies, 46442 participants; HR 0.90, 95% CI 0.83 to 0.98; $I^2 = 0\%$, *high certainty evidence*), major adverse cardiovascular events 3-point (MACE-3P) (10 studies, 40866 participants; HR 0.88, 95% CI 0.82 to 0.95; $I^2 = 28\%$, *high certainty evidence*), acute kidney injury (AKI) (8 studies, 24187 participants; HR 0.76, 95% CI 0.66 to 0.89; $I^2 = 0\%$, *high certainty evidence*), and kidney composite outcome (8 studies, 34788 participants; HR 0.60, 95% CI 0.52 to 0.70; $I^2 = 46\%$, *high certainty evidence*), compared to placebo. SGLT2 inhibitors probably increase diabetic ketoacidosis (9 studies, 31442 participants; HR 2.22, 95% CI 1.18 to 4.16; $I^2 = 6\%$, *moderate certainty evidence*) and genital infection (13 studies, 14843 participants; HR 2.6, 95% CI 2.02 to 3.34; $I^2 = 0\%$, *moderate certainty evidence*) compared to placebo (Table 24.4).

Glucagon-like Peptide-1 Receptor Agonists

Glucagon-like peptide-1 (GLP-1) agonists have been shown in experimental models to reduce albuminuria, decrease mesangial expansion and glomerular basement membrane

Table 24.4 SGLT2 versus placebo in people with type 2 diabetes mellitus and chronic kidney disease

Outcomes	Relative effect (95% CI)	Absolute effect (95% CI)	No. of Participants(No. of studies)	Quality of the evidence(GRADE)	Conclusions
All-cause mortality Mean follow-up: 37 months	HR 0.88 (0.82 to 0.95)	10 fewer per 1,000(from 16 fewer to 4 fewer)	31523 (17 studies)	High	SGLT2 inhibitors decrease all-cause mortality
Cardiovascular mortality Mean follow-up: 26 months	HR 0.90 (0.83 to 0.98)	7 fewer per 1,000(from 12 fewer to 1 fewer)	46442 (12 studies)	High	SGLT2 inhibitors decrease cardiovascular mortality
MACE-3P Mean follow-up: 31 months	HR 0.88 (0.82 to 0.95)	15 fewer per 1,000(from 23 fewer to 6 fewer)	40866 (10 studies)	High	SGLT2 inhibitors decrease MACE-3P
Kidney composite outcome Mean follow-up: 33 months	HR 0.60 (0.52 to 0.70)	39 fewer per 1,000(from 48 fewer to 29 fewer)	34788 (8 studies)	High	SGLT2 inhibitors decrease kidney composite outcome
AKI Mean follow-up: 30 months	HR 0.76 (0.66 to 0.89)	11 fewer per 1,000(from 15 fewer to 5 fewer)	24187 (8 studies)	High	SGLT2 inhibitors decrease AKI
Diabetic ketoacidosis Mean follow-up: 28 months	HR 2.22 (1.18 to 4.16)	37 more per 1,000(from 5 more to 92 more)	31442 (9 studies)	Moderate	SGLT2 inhibitors probably increases diabetic ketoacidosis
Genital infection Mean follow-up: 18 months	HR 2.6 (2.02 to 3.34)	14 more per 1,000(from 9 more to 21 more)	14843 (13 studies)	Moderate	SGLT2 inhibitors probably increases genital infections

AKI = Acute kidney injury; CI = Confidence interval; HR = Hazard ratio; MACE-3P = Major adverse cardiovascular events 3-point; SGLT2 = Sodium-glucose cotransporter-2

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thickness, confer endothelial protection, and restore podocyte function. The main factors mediating renoprotection include inhibition of protein kinase B signaling, inhibition of NAD(P)H oxidative signaling, increased cAMP and protein kinase A, and reduction in inflammatory cell infiltration and ICAM-1 expression [154, 155]. GLP-1 receptor agonists have also been shown to normalize glomerular hyperfiltration in diabetes through inhibition of atrial natriuretic peptide, which limits afferent arteriolar vasodilation, and inhibition of endothelin, which limits efferent arteriolar vasoconstriction [156]. These positive effects have been replicated in clinical trials with lira- [155], sema- [156], and dula-glutides and lixisenatide all demonstrating a reduction in albuminuria; liraglutide and duraglutide have shown a reduction in the decline of eGFR. Both CV and kidney benefits persist in patients with an eGFR of <60 ml/min.

The secondary kidney outcomes of the LEADER study were reported in 2017 [157]. Of the 9340 patients randomized 20.7% had an eGFR of between 30 and 59 ml/min (stage 3 CKD), 26.3% had moderately increased urine protein, and 10.5% had macroproteinuria. The kidney outcome, i.e. a composite of new-onset persistent severely increased urine protein, persistent doubling of the serum creatinine level, kidney failure, or death due to kidney disease, occurred in fewer participants in the liraglutide group than in the placebo group (268 of 4668 patients vs. 337 of 4672, HR 0.78, 95% CI 0.67–0.92, $P = 0.003$). This result was driven primarily by the new onset of persistent severely increased urine protein, which occurred in fewer participants in the liraglutide group than in the placebo group (161 vs. 215 patients, HR 0.74, 95% CI 0.60– 0.91, $P = 0.004$). Liraglutide administration was associated with a significant reduction in albuminuria, with nearly 25% lower likelihood of development of severely increased urine protein, and with the uACR approximately 20% lower among treated people, regardless of the baseline level of eGFR. No significant effect on eGFR was found with liraglutide, although both those receiving and not receiving the drug showed a decline in eGFR from approximately 75 to 65 ml/min/1.73 m^2 over the 48-month period of observation. In subgroup analyses presented at the EASD in October 2018, it was demonstrated that the cardiovascular benefit was more significant in patients with an eGFR between 30 and 60 ml/min/1.73m^2 compared to those with higher levels of eGFR [158].

Similarly, in the Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes trial (SUSTAIN-6), persistent severely increased urine protein developed among 2.7% of those receiving semaglutide, but among 4.9% of those receiving placebo. Fewer subjects treated with semaglutide overall reached the composite endpoint of severely increased urine protein, doubling of serum creatinine to reach an eGFR of less than 45 ml/min/m^2 or persistent renal replacement therapy. Overall the HR of developing new or worsening nephropathy was 0.64 (CI 0.46–0.88, $P < 0.005$) [159].

The ELIXA trial investigated the effects of lixisenatide in acute coronary syndrome (ACS) [160]. Although no benefit was observed in CV outcomes, secondary analyses demonstrated a reduction in severely increased urine protein in the lixisenatide-treated patients ($P < 0.01$) with a modest reduction in moderately increased urine protein ($P < 0.05$) [161]. Despite no benefit in eGFR being observed with lixisenatide treatment in the overall population, in the subgroup with an eGFR of between 30 and 59 ml/min/1.73m^2 a slowing in the rate of decline in eGFR was observed [157].

AWARD-7 assessed the effect of dulaglutide versus insulin glargine in a study population enriched with DKD (mean eGFR 38 ml/min/1.73 m^2). A slowing in the rate of decline of GFR, measured by cystatin C and a reduction in albuminuria, was observed in patients treated with either 1.5 or 1.75 mg of dulaglutide/day. The benefit for dulaglutide was more pronounced in patients with severely increased urine protein compared to those with moderately increased urine protein. These benefits were independent of glycemic control. A greater weight loss and lower incidence of hyperglycemia were also observed in the dulaglutide-treated patients [162]. A Cochrane systematic review which is undergoing an update [153]reported that GLP-1 agonists decrease all-cause mortality (6 studies, 3363 participants; HR 0.76, 95% CI 0.62 to 0.93; $I^2 = 0\%$, *high certainty evidence*), cardiovascular mortality (4 studies, 3138 participants; RR 0.70, 95% CI 0.54 to 0.92; $I^2 = 0\%$, *high certainty evidence)*, probably decrease MACE-3P (6 studies, 31245 participants; HR 0.83, 95% CI 0.75 to 0.93; $I^2 = 55\%$, *moderate certainty evidence*), decrease kidney composite outcome (2 studies, 4357 participants; HR 0.83, 95% CI 0.74 to 0.93; $I^2 = 0\%$, *high certainty evidence*), and probably make little or no difference on AKI (2 studies, 2482 participants; HR 0.83, 95% CI 0.62 to 1.11; $I^2 = 0\%$, *moderate certainty evidence*) compared to placebo or standard care (Table 24.5).

Dipeptidyl Peptidase 4 Inhibitors

Dipeptidyl peptidase (DPP) inhibitors are increasingly used in the CKD population to achieve optimal glycemic control. DPP-4 is involved in the development of kidney fibrosis process via catalytic-dependent or -independent mechanisms [163]. DPP-4 exhibits several important biological functions that predict that inhibition of DPP-4

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Table 24.5 GLP-1 versus placebo/standard care in people with type 2 diabetes mellitus and chronic kidney disease

Outcomes	Relative effect (95% CI)	Absolute effect (95% CI)	No. of Participants (No. of studies)	Quality of the evidence(GRADE)	Conclusions
All-cause mortality Mean follow-up: 5 months	HR 0.76 (0.62 to 0.93)	28 fewer per 1,000(from 45 fewer to 8 fewer)	3363 (6 studies)	High	GLP-1 agonists decrease all-cause mortality
Cardiovascular mortality Mean follow-up: 20 months	RR 0.70 (0.54 to 0.92)	25 fewer per 1,000(from 38 fewer to 7 fewer)	3138 (4 studies)	High	GLP-1 agonists decrease cardiovascular mortality
MACE-3P Mean follow-up: 44 months	HR 0.83 (0.75 to 0.93)	42 fewer per 1,000(from 62 fewer to 17 fewer)	31245 (6 studies)	Moderate	GLP-1 agonists probably decrease MACE-3P
Kidney composite outcome Mean follow-up: 4.6 years	HR 0.83 (0.74-0.93)	12 fewer per 1,000(from 22 fewer to 0 fewer)	4357 (2 studies)	High	GLP-1 agonists decrease kidney composite outcome
AKI Mean follow-up: 26 months	HR 0.83 (0.62 to 1.11)	1 fewer per 1,000(from 3 fewer to 1 more)	2482 (2 studies)	Moderate	GLP-1 agonists probably make little or no difference on AKI

AKI = Acute kidney injury; CI = Confidence interval; GLP-1 = glucagon-like peptide 1 receptor; HR = Hazard ratio; MACE-3P = Major adverse cardiovascular events 3-point; RR = Relative risk

should reduce inflammation and fibrosis. More than 30 potential substrates for DPP-4 have been identified, including GLP-1, glucose-dependent insulinotropic peptide (GIP), high mobility group protein 1 (HMGB1), brain natriuretic peptide, neuropeptide Y, and meprin [163–169]. DPP-4 and integrin-β1 interactions induce profibrotic cellular signaling and endothelial mesenchymal transition [170]. DPP4 inhibitors have experimentally been shown to be renoprotective, with in vitro and animal data suggestive of inhibition of inflammatory and fibrotic responses that would otherwise drive kidney injury [171–174]. DPP-4 inhibition induces miR-29, a key antifibrotic miR, integrin β1, and IFN-γ. Suppression of IFN-γ results in the induction of FGF 1, which induces miR-let-7. Increased levels of miR-let-7 suppress the expression of TGFbR1, resulting in the auto amplification of miR-29s [163].

Many preclinical studies have confirmed the potential renoprotective effects of DPP-4 inhibitors in multiple kidney injury models, including diabetic [175–178] and non-diabetic models of nephropathy [179–182]. Thus far, no clinical trial has revealed beneficial effects of DPP-4 inhibitors on kidney hard outcomes.

Smaller and retrospective clinical studies demonstrated a benefit in favor of DPP4 inhibitors reducing albuminuria [183], but cardiovascular endpoint studies where kidney outcomes have been reported have shown no benefit compared to that of placebo for saxagliptin (SAVOR-TIMI) [184], sitagliptin (TECOS) [185], alogliptin (EXAMINE) [186], or linagliptin. The CARMELINA trial compared DPP-4 inhibitor linagliptin against placebo for cardiovascular safety as specified by the FDA. The CARMELINA trial is unique as 60% of the participants had CKD, with patients enrolled down to an eGFR of 15 ml/min/1.73 m^2. Linagliptin did not increase the risk of CV events or heart failure and hence was deemed safe in individuals with DKD. Although linagliptin showed a significant reduced risk for progression to albuminuria (HR 0.86, 95% CI 0.78–0.96, $P < 0.0034$), it had no impact on the composite kidney endpoint of a sustained >40% reduction in eGFR, kidney failure, or death due to kidney disease (HR 1.04, 95% CI 0.89–1.22) [187]. A Cochrane systematic review which is undergoing an update [153] reported that DPP-4 inhibitors make little or no difference on all-cause mortality (9 studies, 11509 participants; HR 0.92, 95% CI 0.80 to 1.05; $I^2 = 0\%$, *high certainty evidence*), cardiovascular mortality (4 studies, 7569 participants; HR 0.98, 95% CI 0.83 to 1.15; $I^2 = 0\%$, *high certainty evidence*), MACE-3P (4 studies, 14441 participants; HR 1.00, 95% CI 0.92 to 1.10; $I^2 = 0\%$, *high certainty evidence*), kidney composite outcome (2 studies, 9555 participants; HR 1.08, 95% CI 0.89 to 1.31; $I^2 = 33\%$, *high certainty evidence*), and may make little or no difference on AKI (2 studies, 7112 participants; RR 0.95, 95% CI 0.73 to 1.24; $I^2 = 0\%$, *low certainty evidence*) compared to placebo (Table 24.6).

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Table 24.6 DPP-4 versus placebo in people with type 2 diabetes mellitus and chronic kidney disease

Outcomes	Relative effect (95% CI)	Absolute effect (95% CI)	No. of Participants (No. of studies)	Quality of the evidence(GRADE)	Conclusions
All-cause mortality Mean follow-up: 15 months	HR 0.92 (0.8 to 1.05)	8 fewer per 1,000(from 20 fewer to 5 more)	11509 (9 studies)	High	DPP-4 inhibitors make little or no difference on all-cause mortality
Cardiovascular mortality Mean follow-up: 40 months	HR 0.98 (0.83 to 1.15)	1 fewer per 1,000(from 12 fewer to 11 more)	7569 (4 studies)	High	DPP-4 inhibitors make little or no difference on cardiovascular mortality
MACE-3P Mean follow-up: 44 months	HR 1.0 (0.92 to 1.10)	3 more per 1,000(from 11 fewer to 16 more)	14441 (4 studies)	High	DPP-4 inhibitors make little or no difference on MACE-3P
Kidney composite outcome Mean follow-up: 40 months	HR 1.08 (0.89 to 1.31)	8 more per 1,000(from 11 fewer to 29 more)	9555 (2 studies)	High	DPP-4 inhibitors make little or no difference on kidney composite outcome
AKI Mean follow-up: 20 months	RR 0.95 (0.73 to 1.24)	12 more per 1,000(from 41 fewer to 202 more)	7112 (2 studies)	Low	DPP-4 inhibitors may make little or no difference on AKI

AKI = Acute kidney injury; CI = Confidence interval; DPP-4 = Dipeptidyl peptidase 4; HR = Hazard ratio; MACE-3P = Major adverse cardiovascular events 3-point; RR = Relative risk

Metformin

Metformin is a widely used and effective hypoglycemic drug that remains the first line of treatment for individuals with type 2 DM. The mechanisms underlying improved glycemic control are complex and not fully understood. Metformin reduces hepatic gluconeogenesis and increases peripheral glucose sensitivity. Although not tested in clinical trials, experimental evidence suggests it may limit kidney disease via both AMP-activated protein kinase (AMPK)-dependent and AMPK-independent mechanisms and by inhibition of mitochondrial respiration [188]. Current guidelines recommend metformin monotherapy should be started when a diagnosis of type 2 DM is made (in different jurisdictions a failure of lifestyle interventions also needs to be demonstrated), unless there are contraindications [189, 190]. This recommendation is based on its efficacy in lowering HbA1c, its safety profile, affordability, negligible risk of hypoglycemia, and lack of weight gain. Compared to sulfonylureas, metformin monotherapy has comparable HbA1c-lowering effects, glycemic durability [191], lower risks of hypoglycemia [192], less weight gain [192, 193], and in observational studies a lower CV risk [193]. In the UKPDS, metformin was shown to confer CV benefit in newly diagnosed overweight included individuals with type 2 DM [194]. However, conflicting evidence from a meta-analysis of metformin trials has been presented [195, 196]. Metformin has well-documented gastrointestinal side effects. Hence, it is recommended to commence on low dose with gradual dose escalation based on tolerability. Metformin is associated with vitamin B12 deficiency and periodic testing of vitamin B12 levels should be considered, especially in those with anemia or peripheral neuropathy [197]. Combination glucose-lowering therapy is often recommended by guidelines with insulin, DPP-4 inhibitors, GLP-1 receptor agonists or SGLT2 inhibitors over other antihyperglycemic agents as these combinations are associated with less hypoglycemia and weight gain provided there are no contraindications or barriers to affordability or access [189, 190].

Adding metformin to insulin therapy may reduce insulin requirements and improve metabolic control in patients with type 1 DM. Evidence suggests the use of metformin, in addition to insulin therapy in type 1 DM, results in reduced insulin requirements [198], weight reduction [199], improvement in lipid profiles [200] but no improvement in glycemic control or CV outcomes [198, 200].

Metformin can lead to rises in serum lactate due to conversion of glucose to lactate by the intestinal mucosa and reduced uptake of lactate in the liver [201–203]. The molecular weight (MW) of metformin is 129.16 g/mol [204] (MW of creatinine is 113.12 g/mol). Metformin is nonprotein-bound and is primarily eliminated unchanged by the kidneys and therefore CKD is associated with higher drug levels that could increase the risk of lactic acidosis [205, 206]. However, significant lactic acidosis associated with metformin use is rare. A small

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nonplacebo-controlled study involving 35 patients on automated peritoneal dialysis with insulin-dependent type 2 DM, receiving 0.5–1 g daily dose of metforminm, found no incidence of lactic acidosis, although a higher number of individuals receiving metformin had plasma lactate levels >2 mmol/l [204]. The FDA recently revised the label for metformin to reflect its safety in patients with eGFR ≥30 ml/min/1.73 m^2 [207].

In a meta-analysis of 347 comparative trials and cohort studies there was no evidence to suggest the use of metformin in CKD stage 3b or higher enhances the risk for lactic acidosis. In fact, no cases of lactic acidosis were identified in 70 490 patient-years of metformin use [208]. Individual studies have reported crude incidences of 3.3–10.4 cases per 100 000 patient-years [209–212], which is comparable to rates of lactic acidosis in individuals with type 2 DM taking nonmetformin agents [210, 213]. In the only randomized control trial, Rachmani et al. randomly assigned 393 patients with type 2 DM with a serum creatinine of 130–200 μmol/l to continue or stop metformin [214]. The authors demonstrated a close correlation between serum creatinine and lactate levels ($r = 0.78$, $P < 0.001$), which was not shown in other studies [215, 216]. Hung et al. reported metformin use in 3254 patients with advanced CKD approaching kidney failure (creatinine >530 μmol/l) was not associated with a significantly greater risk of metabolic acidosis (adjusted HR 1.30, 95% CI 0.88–1.93) [217]. Richy et al. examined the Datalinkage records of 77 601 patients in UK treated with metformin for type 2 DM between 2007 and 2012 [211], and found no difference in the incidence of lactic acidosis in patients with more advanced CKD compared to those with normal kidney function. Eppenga et al. investigated a larger cohort of 223 968 patients with type 2 DM prescribed metformin between 2004 and 2012 [212], and reported no difference in incidence of lactic acidosis between metformin or nonmetformin users if eGFR ≥60 ml/min, but the risk was significantly higher for metformin users with an eGFR <60 ml/min (adjusted HR 6.37, 95% CI 1.48–27.5). Interestingly, the risk of lactic acidosis of those with eGFR 30–44 ml/min was comparable to those with an eGFR of 45–59 ml/min.

The existing evidence is largely extrapolated from studies involving participants with normal or mildly impaired kidney function. There is a lack of objective outcome data to guide the use of metformin in the CKD population itself and further studies are needed. For the CKD population, the question is not whether to start metformin but whether to continue. In patients who have been well maintained on metformin, particularly those who are overweight, the evidence supporting its routine withdrawal upon reaching an eGFR of 30 ml/min is equivocal [218–220].

Sulfonylureas

Sulfonylureas bind ATP-dependent K+ channels on cell membranes of the pancreatic beta cells which, through increasing intracellular calcium, leads to increased insulin secretion [221]. Sulfonylurea use in CKD requires careful attention to dosing to avoid hypoglycemia [222, 223]. However, if a sulfonylurea is to be added to metformin, gliclazide should be considered as first choice as it is associated with a lower risk of hypoglycemia [222, 224]. Glyburide is extensively metabolized in the liver into several active metabolites that are excreted by the kidney and is not recommended for use in CKD. Glipizide is metabolized by the liver into several inactive metabolites, and its clearance and elimination half-life are not affected by a reduction in eGFR, thus dose adjustments in patients with CKD are not necessary. Although glimepiride is associated with less hypoglycemia when compared with glyburide, it has similar rates of hypoglycemia when compared to other sulfonylureas. No studies have demonstrated a kidney benefit for the use of sulfonylureas, with conflicting data on CV events and mortality. A network meta-analyses of 14 464 patients concluded that gliclazide and glimepiride were associated with a lower risk of all-cause and cardiovascular-related mortality compared with glibenclamide [225]. A prospective cohort study from the UK Clinical Practice Research Datalink, using the prevalent new metformin user, matched 1 : 1 with patients adding or switching to sulfonylureas. The study looked at 77 138 metformin new users of whom 25 699 added or switched to sulfonylureas between 1998 and 2013. During a mean follow-up of 1.1 years, sulfonylureas were associated with an increased risk of myocardial infarction (HR 1.26, 95% CI 1.01–1.56), all-cause mortality (HR 1.28, 95% CI 1.15–1.44), and severe hypoglycemia (HR 7.60, 95% CI 4.64–12.44) compared with metformin monotherapy [226]. Given the lack of observational data to support a differentially positive effect in patients with DKD it is unlikely that sulfonylureas will be further studied.

Thiazolidinediones

Thiazolidinediones (TZDs) are a class of oral hypoglycemic agents that improve glycemic control primarily by decreasing insulin resistance, thus improving the insulin sensitivity of the liver and peripheral tissues. They have also been implicated in reducing pancreatic beta cell apoptosis, and are predominantly metabolized by the liver. Despite the demonstrated anti-inflammatory and antifibrotic effects in experimental models [227–230] and lack of a need for dosage adjustments in patients with CKD, TZD use is generally avoided in CKD due to side effects such as refractory fluid retention, a reported increase in heart failure, and increased fracture risk.

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The PROspective pioglitAzone Clinical Trial (PROactive) study randomized 5238 high-risk subjects with type 2 DM with established macrovascular disease to pioglotazone or matching placebo [231]. In a mean follow-up of 34.5 months, the pioglitazone-treated group had fewer secondary endpoints (composite of all-cause mortality, nonfatal myocardial infarction, and stroke) (301 vs. 358, HR 0.84, 95% CI 0.72–0.98, $P = 0.03$) when compared with the placebo. The incidence of hospitalization with heart failure or mortality rates from heart failure did not differ between groups. In a follow-up analysis of the PROactive study, although pioglitazone (5.7%) was associated with more serious heart failure events during the study than placebo (4.1%) ($P = 0.007$), pioglitazone was associated with lower fatal/nonfatal MI (28% risk reduction [RR], $P = 0.045$) and ACS (37% RR, $P = 0.04$) compared to placebo in the subgroup of participants with significant heart failure [232]. A post hoc analysis investigated the relationship between CKD and incident CVD in this population as well as the effects of pioglitazone treatment on recurrent CVD. CKD, defined as an eGFR <60 ml/min per 1.73 m^2, was present in 597 (11.6%) of 5154 patients. More patients with CKD reached the primary composite endpoint (all-cause mortality, acute myocardial infarction (AMI), stroke, ACS, coronary/carotid arterial intervention, leg revascularization, or amputation above the ankle) than patients without CKD (27.5% vs. 9.6%, $P < 0.0001$) as well as secondary composite endpoint (defined above). A greater decline in eGFR was observed in the pioglitazone-treated group (between-group difference 0.8 ml/min/1.73 m^2/year) than with placebo [233].

The RECORD study randomized 4458 individuals with type 2 DM with inadequate control while on metformin or sulfonylurea in combination with rosiglitazone showed at 18 months that HbA1c reduction is similar between rosiglitazone added to metformin or sulfonylureas [234]. In a further interim analysis (3.75 years follow-up) the same group presented outcomes and deaths from cardiovascular causes in all 4447 subjects. Although there were no statistically significant differences between the rosiglitazone versus control groups regarding myocardial infarction and death from CV causes or all-cause, there were more people with heart failure in the rosiglitazone group than in the control group (HR 2.15, 95% CI 1.30– 3.57) [235]. The final analysis of the RECORD study, with a mean 5.5-year follow-up, showed that addition of rosiglitazone to glucose-lowering therapy in people with type 2 DM increased the risk of heart failure and fractures, especially in women. The addition of rosiglitazone to the therapeutic regimen of people with type 2 DM was not associated with reduced risk of overall cardiovascular morbidity or mortality compared with standard glucose-lowering medications. A meta-analysis that included 20 191 subjects with either prediabetes or type 2 DM who had CHF examined the risk of exacerbation of congestive cardiac failure (CCF) in those taking TZDs compared with control and found the risk of CCF was higher in people given TZDs (RR 1.72, 95% CI 1.21–2.4, $P = 0.002$). There was no heterogeneity of effect across the seven studies, suggesting that it is a class effect of TZDs. However, a higher rate of CV death was not observed [236]. There were no kidney outcomes reported in these studies. A Cochrane systematic review which is undergoing an update [153] reported that thiazolidinediones may make little or no difference on all-cause mortality (2 studies, 147 participants; RR 0.35, 95% CI 0.06 to 2.23; $I^2 = 0\%$, *low certainty evidence*) and heart failure (2 studies, 123 participants; RR 0.34, 95% CI 0.01 to 8.13; *low certainty evidence*), compared to placebo or control (Table 24.7).

Blood Pressure Lowering in DKD

Observational studies show a strong relationship between a higher level of BP and an increased risk of kidney failure and worsening kidney function in DKD. Optimal

Table 24.7 Thiazolidinediones versus placebo/control in people with type 2 diabetes mellitus and chronic kidney disease

Outcomes	Relative effect (95% CI)	Absolute effect (95% CI)	No. of Participants (No. of studies)	Quality of the evidence(GRADE)	Conclusions
All-cause mortality Mean follow-up: 25 weeks	RR 0.35 (0.06 to 2.23)	36 fewer per 1,000(from 52 fewer to 68 more)	147 (2 studies)	Low	Thiazolidinediones may make little or no difference on all-cause mortality
Heart failure Mean follow-up: 18 months	RR 0.34 (0.01 to 8.13)	11 fewer per 1,000(from 16 fewer to 114 more)	123 (2 studies)	Low	Thiazolidinediones may make little or no difference on heart failure
Kidney failure	-	-	-	-	No studies were found that looked at kidney failure

CI = Confidence interval; RR = Relative risk

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BP control is accepted as an important therapy in the prevention and progression of CKD in diabetes, although the optimal targets for BP in patients DKD have not been determined [237–241].

The UKPDS study suggested that a target BP of <150/85 mmHg was associated with a reduction in microvascular events, including kidney outcomes [194]. In the Systolic Hypertension in Europe (Syst-Eur) trial, a target systolic BP of <150 mmHg was associated with a lower incidence of proteinuria among those with diabetes and in the overall study group was associated with fewer people developing a creatinine >177 mmol/l [242]. The Appropriate Blood Pressure Control in Diabetes (ABCD) normotensive study found that achieving a systolic BP of <130 mmHg was associated with fewer people developing moderately increased urine protein and reduced risk of progression from moderately to severely increased urine protein [243]. A study in type 1 DM found that a target mean arterial pressure of 92 mmHg (125/75) was associated with a reduction in proteinuria [244].

Intensive Versus Standard BP Lowering in DKD

The ACCORD BP trial examined whether an spontaneous bacterial peritonitis (SBP) of <120 mmHg in patients with type 2 DM at high CV risk provided greater cardiovascular protection than an SBP of 130–140 mmHg [245]. The study did not find a benefit in the primary endpoint (i.e. nonfatal MI, nonfatal stroke, and cardiovascular death) comparing intensive BP treatment (mean BP achieved 119/64 mmHg on 3.4 medications) with standard treatment (mean BP achieved 143/70 mmHg on 2.1 medications). Stroke was significantly reduced in the intensive BP treatment groups. The ACCORD BP study found less progression of proteinuria in the intensive BP lowering group, but this was associated with increased risk of AKI events [245]. A follow-up analysis found the intensive BP/intensive glycemia, intensive BP/standard glycemia, and standard BP/intensive glycemia groups all showed benefit for reducing the risk of major CVD when compared to the standard glycemia/standard BP control group in the BP trial [246].

In ADVANCE, the intensive BP intervention arm (a single-pill, fixed-dose combination of perindopril and indapamide) showed a significant reduction in the risk of the primary composite endpoint (major macrovascular or microvascular event) and in the risk of death from any cause and of death from cardiovascular causes [247]. Compared with the placebo group, the patients in the intensive BP lowering arm experienced an average reduction of 5.6 mmHg in SBP and 2.2 mmHg in diastolic blood pressure (DBP). The ADVANCE-ON study reported that the reductions in the risk of all-cause mortality in the intensive arm were attenuated but remained significant [130]. The Hypertension Optimal Treatment (HOT) trial included patients with and without diabetes and compared DBP targets of ≤90, ≤85, and ≤80 mmHg. Post hoc analyses found cardiovascular benefit with more intensive targets in the subpopulation with diabetes [248].

A meta-analysis of five RCTs enrolled 7312 adults with type 2 DM comparing intensive BP targets (upper limit of 130 mmHg systolic and 80 mmHg diastolic) with standard targets (upper limit of 140–160 mmHg systolic and 85–100 mmHg diastolic) and found no significant reduction in mortality or nonfatal MI. There was a statistically significant 35% RR reduction in stroke with intensive targets, but the absolute risk reduction was only 1% and intensive targets were associated with an increased risk for adverse events such as hypotension and syncope [249]. The threshold of BP lowering in diabetics with CKD remains controversial [250].

Pharmacotherapy for BP Lowering

RAAS Blockade

RAAS blockade using various drugs, including angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), direct renin inhibitors, and mineralocorticoid receptor antagonists have shown efficacy in animal models of DKD. In humans, RAAS inhibition has proved to be the single most effective therapy for slowing the progression of DKD.

The CAPTOPRIL study was the first large trial to examine the effect of ACE inhibitors on the progression of advanced DKD. The study randomly assigned 409 patients with type 1 DM, overt proteinuria (protein excretion ≥500 mg/day), and reduced kidney function to captopril 25 mg three times a day or matching placebo. There was a 48% reduction in risk for doubling of serum creatinine concentration and a 50% reduction in the composite endpoint of death, dialysis therapy, or transplantation [251]. This trial established the efficacy of ACE inhibitors independent of BP control in slowing the progression of DKD in patients with type 1 DM and overt proteinuria. The other trials using RAAS blockade in patients with type 1 DM including the (Renin-Angiotensin System Study [RASS] [252], Diabetic Retinopathy Candesartan Trial [DIRECT] -Prevent 1, and DIRECT-Protect 1) [253] failed to show that RAAS blockade prevented the development of moderately increased urine protein in those with normoalbuminuria at baseline.

The Effect of Irebesrtan in the Development of Diabetic Nephropathy in Patients With T2DM (IRMA-2) trial randomly assigned 590 patients with type 2 DM and moderately increased urine protein to irbesartan 150 mg daily,

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irbesartan 300 mg daily or matching placebo with follow-up for 2 years to determine the effect of irbesartan in prevention of new onset of overt proteinuria. Irbesartan reduced the risk for the development of overt proteinuria (defined as albumin excretion >200 mg/day) in a dose-dependent benefit [254]. The Irbesartan in Diabetic Nephropathy Trial (IDNT) [144] and the Reduction of Endpoints in Non Insuline Dependent Diabetes Mellitus (NIDDM) with the Angiotensin II Antagonist Losartan (RENAAL) [143] study independently showed irbesartan and losartan, respectively, can delay the progression of DKD in patients with type 2 DM, overt proteinuria, and reduced kidney function. IDNT randomly assigned 1715 participants to irbesartan, amlodipine, or placebo with follow-up for a mean of 2.6 years. BP was targeted at <135/85 mmHg and was achieved with agents in classes other than those under study. Independent of BP control, irbesartan reduced the risk for the composite outcome of doubling of serum creatinine concentration, kidney failure, or death as compared to amlodipine or placebo. The RENAAL trial followed up 1513 patients with type 2 DM and overt proteinuria for a mean of 3.4 years and demonstrated that losartan 100 mg daily was superior to placebo to reduce the risk for the same composite endpoint as in IDNT [143]. Taken together, these studies provide robust evidence supporting the benefit independent of BP lowering of RAS-blocking medication on slowing the progression of DKD. Despite the dramatic benefit with ARB therapy, many participants on ARB therapy still ended up with kidney failure, therefore novel therapy and drug development is required for prevention of progressive DKD.

In patients with type 2 DM with early and incipient nephropathy, mixed results were observed. In the Heart Outcomes Prevention Evaluation (HOPE) trial, the use of ramipril was not effective in preventing new onset microalbuminuria [255]. The Bergamo Nephrologic Diabetes Complications Trial (BENEDICT) study randomly assigned patients to one of four arms (placebo, trandolapril, verapamil, or trandolapril plus verapamil) for at least 3 years with a goal BP <120/80 mmHg. The two arms containing trandolapril showed a benefit in preventing the development of albuminuria, with post hoc analyses suggesting that the effect was independent of BP reduction [256]. The Randomized Olmesartan and Diabetes Microalbuminuria Prevention (ROADMAP) trial followed up 4449 participants for a median of 3.2 years. There was a statistically significant difference in BP between the olmesartan and placebo arms. The primary analysis of the trial showed that olmesartan prevented or delayed the onset of moderately increased urine protein, with moderately increased urine protein developing in 8.2% versus 9.8% of participants (olmesartan vs. placebo). However, the olmesartan group had lower BPs and an increase in CV deaths [257], although the study was not powered to assess this as an endpoint. In recent years, new studies have been conducted in people with DKD, comparing RAAS blockade with placebo or no treatment.A Cochrane systematic review which is undergoing an update [258] reported that ACE inhibitors may make little or no difference on all-cause mortality (24 studies, 7413 participants; RR 0.91, 95% CI 0.73 to 1.15; I^2 = 23%, *low certainty evidence*), fatal or nonfatal stroke (2 studies, 4944 participants; RR 1.02, 95% CI 0.80 to 1.31; I^2 = 0%, *low certainty evidence*) and fatal or nonfatal myocardial infarction (3 studies, 5100 participants; RR 0.79, 95% CI 0.57 to 1.09; I^2 = 0%, *low certainty evidence*) compared to placebo or no treatment. The effects of ACE inhibitor on cardiovascular mortality and doubling of serum creatinine were very uncertain (Table 24.8).

The same Cochrane review reported that ARB may make little or no difference on all-cause mortality (11 studies, 4260 participants; RR 0.99, 95% CI 0.85 to 1.16; I^2 = 0%, *low certainty evidence*), and has uncertain effects on cardiovascular mortality (6 studies, 878 participants; RR 3.36, 95% CI 0.93 to 12.07; *low certainty evidence*), fatal or nonfatal stroke (2 studies, 619 participants; RR 0.76, 95% CI 0.32 to 1.77; I^2 = 0%, *low certainty evidence*) and fatal or nonfatal myocardial infarction (2 studies, 619 participants; RR 0.43, 95% CI 0.11 to 1.65; *low certainty evidence*), and may prevent doubling of serum creatinine (4 studies, 3280 participants; RR 0.84, 95% CI 0.72 to 0.97; I2 = 37%, *low certainty evidence*) compared to placebo or no treatment (Table 24.9).

Combination Therapy

In the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack (ALLHAT) trial subgroup, 13 101 participants with type 2 DM were randomly assigned to chlorthalidone, amlodipine (dihydropyridine calcium channel blocker [CCB]) or lisinopril. Despite the chlorthalidone-treated group having a lower systolic BP when compared with lisinopril or amlodipine, no difference in the primary endpoint of combined fatal coronary heart disease or nonfatal or fatal MI (HR 0.97, 95% CI 0.86–1.10) was seen between amlodipine and chlorthalidone. The Avoiding Cardiovascular events through Combination therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial compared benazepril/amlodipine combination treatment with benazepril/thiazide therapy [259]. The trial enrolled 6946 high-risk participants with type 2 DM and 2842 participants with high CV and kidney risk. The primary endpoint was a composite of MI, stroke, CV death, hospitalization for angina, resuscitated cardiac arrest, and coronary revascularization. Benazepril/amlodipine reduced occurrence of the primary event compared to benazepril/thiazide in all subjects with diabetes (8.8% vs. 11%; HR 0.79, 95%

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Table 24.8 ACEi versus placebo/no treatment in people with diabetic kidney disease.

Outcomes	Relative effect (95% CI)	Absolute effect (95% CI)	No. of Participants (No. of studies)	Quality of the evidence(GRADE)	Conclusions
All-cause mortality Mean follow-up: 2.9 years	RR 0.91 (0.73 to 1.15)	11 fewer per 1000 (34 fewer to 19 more)	7413 (24 studies)	Low	ACEi may make little or no difference on all-cause mortality compared to placebo/no treatment
Cardiovascular mortality Mean follow-up: 2.3 years	RR 0.67 (0.13 to 3.57)	16 fewer per 1000 (43 fewer to 126 more)	5625 (17 studies)	Very low	It is very uncertain whether ACEi makes any difference on cardiovascular mortality compared to placebo/no treatment
Doubling of serum creatinine Mean follow-up: 4 years	RR 0.69 (0.47 to 1.01)	13 fewer per 1000 (23 fewer to 0)	6702 (8 studies)	Very low	It is very uncertain whether ACEi makes any difference on doubling of serum creatinine compared to placebo/no treatment
Fatal or nonfatal stroke Mean follow-up: 7 years	RR 1.02 (0.80 to 1.31)	1 more per 1000 (9 fewer to 15 more)	4944 (2 studies)	Low	ACEi may make little or no difference on fatal or nonfatal stroke compared to placebo/no treatment
Fatal or nonfatal myocardial infarction Mean follow-up: 3.2 years	RR 0.79 (0.57 to 1.09)	6 fewer per 1000 (13 fewer to 3 more)	5100 (3 studies)	Low	ACEi may make little or no difference on fatal or nonfatal myocardial infarction compared to placebo/no treatment

ACEi = Angiotensin converting enzyme inhibitors; CI = Confidence interval; RR = Relative risk

Table 24.9 ARB versus placebo/no treatment in people with diabetic kidney disease.

Outcomes	Relative effect (95% CI)	Absolute effect (95% CI)	No. of Participants (No. of studies)	Quality of the evidence(GRADE)	Conclusions
All-cause mortality Mean follow-up: 2.2 years	RR 0.99 (0.85 to 1.16)	1 fewer per 1000 (20 fewer to 22 more)	4260 (11 studies)	Low	ARB may make little or no difference on all-cause mortality compared to placebo/no treatment
Cardiovascular mortality Mean follow-up: 1.6 years	RR 3.36 (0.93 to 12.07)	17 more per 1000 (0 to 78 more)	878 (6 studies)	Low	ARB have uncertain effects on cardiovascular mortality compared to placebo/no treatment
Doubling of serum creatinine Mean follow-up: 2.9 years	RR 0.84 (0.72 to 97)	45 fewer per 1000 (79 fewer to 8 fewer)	3280 (4 studies)	Low	ARB may prevent doubling of serum creatinine compared to placebo/no treatment
Fatal or nonfatal stroke Mean follow-up: 2.8 years	RR 0.76 (0.32 to 1.77)	9 fewer per 1000 (26 fewer to 30 more)	619 (2 studies)	Low	ARB have uncertain effects on fatal or nonfatal stroke compared to placebo/no treatment
Fatal or nonfatal myocardial infarction Mean follow-up: 2.8 years	RR 0.43 (0.11 to 1.65)	13 fewer per 1000 (20 fewer to 15 more)	619 (2 studies)	Low	ARB have uncertain effects on fatal or nonfatal myocardial infarction compared to placebo/no treatment

ARB = Angiotensin receptor blockers; CI = Confidence interval; RR = Relative risk

CI 0.68–0.92). In an intention-to-treat post hoc analysis, lower events of CKD progression in the benazepril plus amlodipine group compared to the benazepril plus hydrochlorothiazide group (HR 0·52, 95% CI 0.41–0.65, $P < 0{\cdot}0001$) [260]. Although the peripheral oedema is common among both groups with CKD, angioedema was more frequent in the benazepril plus amlodipine group than in the benazepril plus hydrochlorothiazide group. Based on this evidence, for persons in whom combination therapy with an ACE inhibitor is being considered, a dihydropyridine CCB is preferable to a thiazide/thiazide-like diuretic.

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Combination RAAS blockers or the addition of a renin inhibitor such as alliskerin to an ACE inhibitor or angiotensin 2 receptor blocker has not been a positive strategy to reduce progressive loss of kidney function. On the contrary, three large RCTs (ONTARGET, VA-NEPHROND, and ALTITUDE) have shown such interventions increase risk of AKI and hyperkalemia in individuals with DKD [261–263]. Although the combination of agents that block the RAAS are generally not recommended in the management of DKD, a network meta-analysis has also identified dual RAAS blockade as a promising potential therapy if it can be offered safely [264].

Miniralcorticoid Receptors Inhibitor

Aldosterone blockade reduces CV mortality in patients with heart failure and reduces albuminuria [265–267]. Potential mechanisms of action include promotion of salt and water loss, potentially improving volume and BP management, with antifibrotic and antioxidant effects demonstrated in animal studies. The third-generation mineralocorticoid receptor antagonist finerenone has been shown to reduce albuminuria DKD at 90 days without significant safety concerns. The phase 2 study involved 821 participants with type 2 DM, of whom 36.7% had albuminuria (uACR ≥300 mg/g) and 40.0% had an eGFR of ≤60 ml/min/1.73 m^2. Finerenone demonstrated a dose-dependent reduction in uACR. The prespecified secondary outcome of hyperkalemia leading to discontinuation was not observed in the placebo and low-dose finerenone groups, but showed an increasing incidence with higher doses [267]. The impact of adding a mineralocorticoid receptor antagonist to background standard of care including an ACE inhibitor or ARB is being evaluated in the Efficacy and Safety of Finerenone in Subjects With Type 2 Diabetes Mellitus and Diabetic Kidney Disease (FIDELIO-DKD) [268] and Efficacy and Safety of Finerenone in Subjects With Type 2 Diabetes Mellitus and the Clinical Diagnosis of Diabetic Kidney Disease (FIGARO-DKD) trials [269]. The pre-specified meta-analysis FIDELITY, which included FIDELIO-DKD and FIGARO-DKD trials presented at the European Society of Cardiology 2021 Congress demonstrated that the non-steroidal mineralocorticoid receptor antagonist finerenone in addition to ACE inhibition or ARB in patients with CKD and type 2 DM decreased 4-point MACE (HR 0.86, 95% CI 0.78, 0.95) compared to placebo. Other non-steroidal mineralocorticoid receptor antagonists (apararenone, esaxerenone) have been examined in smaller non kidney and CV outcome based trials. The endpoints of this study consist of a composite of first occurrence of the composite endpoint of onset of kidney failure, a sustained decrease of eGFR ≥40% from baseline over at least 4 weeks, and kidney death (primary endpoint for FIDELIO-DKD and secondary endpoint for FIGARO-DKD study). A Cochrane systematic review which is undergoing an update [270] showed that mineralocorticoid receptor antagonist probably makes little or no effect on all-cause mortality (8 studies, 14293 participants; RR 0.90, 95% CI 0.80 to 1.00; I^2 = 0%, *moderate certainty evidence*), cardiovascular mortality (4 studies, 13366 participants; RR 0.88, 95% CI 0.76 to 1.02; I^2 = 0%, *moderate certainty evidence*), myocardial infarction (3 studies, 13080 participants; RR 0.92, 95% CI 0.75 to 1.13; I^2 = 0%, *moderate certainty evidence*), stroke (5 studies, 14259 participants; RR 0.99, 95% CI 0.82 to 1.2; I^2 = 0%, *moderate certainty evidence*) and kidney failure (3 studies, 13080 participants; RR 0.86, 95% CI 0.73 to 1.01; I^2 = 0%, *moderate certainty evidence*) compared to placebo or no treatment (Table 24.10).

Lipid Lowering

Dyslipidemia is common in people with diabetes and CKD. Individuals with diabetes and CKD typically have lower levels of high-density lipoprotein (HDL) cholesterol, high triglyceride, and low-density lipoprotein cholesterol (LDL-C) levels, hence a more atherogenic profile. The evidence that low LDL-C concentration reduces the risk of CV events in patients with diabetes and early CKD generally reflects the evidence reported in the general population.

The Cholesterol Treatment Trialists' (CTT) Collaboration meta-analysis of >170 000 subjects receiving statin found that for every 1.0 mmol/l reduction in LDL-C: low-density lipoprotein-cholesterol there was an approximately 20% reduction in CVD events, regardless of baseline LDL-C [271]. The effects of statins on all fatal and nonfatal CV outcomes were similar for participants with or without diabetes (14 trials, >18 000 participants with diabetes) [272]. The updated CTT meta-analysis of 170 000 participants showed that additional reductions in LDL-C (down to approximately 1.0–2.0 mmol/l) with more intensive therapy further reduced the incidence of major vascular events and that these reductions could be achieved safely, even in individuals with lower baseline LDL-C levels [273]. The IMproved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) showed that the addition of ezetimibe to simvastatin in participants with recent ACS provided CVD event benefit compared to use of simvastatin alone. The event reductions were particularly evident in people with type 2 DM [274].

The data from more advanced CKD are largely derived from the Study of Heart and Renal Protection (SHARP) trial [271]. SHARP randomized 9438 participants >40 years old with CKD (mean eGFR of 27 ml/min/1.73 m^2) to receive simvastatin 20 mg plus ezetimibe 10 mg daily or placebo and

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Table 24.10 Mineralocorticoid versus placebo in people with diabetes mellitus and chronic kidney disease.

Outcomes	Relative effect (95% CI)	Absolute effect| (95% CI)	No. of Participants (No. of studies)	Quality of the evidence(GRADE)	Conclusions
All-cause mortality Mean follow-up: 20 months	RR 0.90 (0.80 to 1.00)	9 fewer per 1,000(from 18 fewer to 0)	14293 (8 studies)	Moderate	Mineralocorticoid receptor antagonist probably makes little or no effect on all-cause mortality
Cardiovascular mortality Mean follow-up: 22 months	RR 0.88 (0.76 to 1.02)	7 fewer per 1,000(from 13 fewer to 1 more)	13366 (4 studies)	Moderate	Mineralocorticoid receptor antagonist probably makes little or no effect on cardiovascular mortality
Myocardial infarction Mean follow-up: 12 months	RR 0.92 (0.75 to 1.13)	2 fewer per 1,000(from 7 fewer to 4 more)	13080 (3 studies)	Moderate	Mineralocorticoid receptor antagonists probably makes little or no difference on myocardial infarction
Stroke Mean follow-up: 16 months	RR 0.99 (0.82 to 1.2)	0 per 1,000 (from 5 fewer to 6 more)	14259 (5 studies)	Moderate	Mineralocorticoid receptor antagonist probably makes little or no effect on stroke
Kidney failure Mean follow-up: 28 months	RR 0.86 (0.73 to 1.01)	6 fewer per 1,000(from 12 fewer to 0)	13080 (3 studies)	Moderate	Mineralocorticoid receptor antagonist probably makes little or no effect on kidney failure

CI = Confidence interval; RR = Relative risk

followed them for 5 years. Thirty-three percent of the patients ($n = 3023$) were receiving maintenance dialysis at randomization and 23% ($n = 2094$) of the participants had diabetes, with equal proportions in the simvastatin plus ezetimibe and placebo groups. The study showed statin plus ezetimibe therapy was associated with a 17% RR in the risk of the major atherosclerotic events (coronary death, myocardial infarction, nonhemorrhagic stroke, or any revascularization) compared with placebo (HR 0.83, 95% CI 0.74–0.94). This finding was attributable in large part to significant reductions in nonhemorrhagic stroke and arterial revascularization procedures. There was no reduction in the risk of all-cause mortality, and among the patients with CKD not treated by dialysis at randomization ($n = 6247$), treatment with simvastatin plus ezetimibe did not reduce the frequency of doubling of the baseline serum creatinine concentration or progression to kidney failure. Although the study was not powered to reliably estimate the effect of treatment on primary outcomes among clinical subgroups, the proportional effect on major atherosclerotic events did not appear to differ between those with or without diabetes.

The 4D study [275] investigated 1255 subjects with type 2 DM receiving maintenance hemodialysis who were randomly assigned to receive 20 mg of atorvastatin or matching placebo daily. During a median follow-up period of 4 years, atorvastatin had no significant effect on the primary endpoint (RR 0.92, 95% CI 0.77–1.10), defined as composite of death from cardiac causes, fatal stroke, nonfatal myocardial infarction, or nonfatal stroke, except that there was an increase in the risk of fatal stroke (RR 2.03, 95% CI 1.05–3.93) among those receiving atorvastatin. Atorvastatin reduced the rate of all cardiac events combined (RR 0.82, 95% CI 0.68–0.99, $P = 0.03$, nominally significant), but not all cerebrovascular events or combined or total mortality. In another study in individuals receiving hemodialysis, the AURORA study [276], 2776 participants (approximately 20% diabetic) were randomized to rosuvastatin 10 mg or matching placebo daily, with a mean follow-up of 3.2 years. A similar effect of rosuvastatin was shown on CV primary outcomes. There was a small but statistically significant increase in the incidence of hemorrhagic stroke in the diabetic patients who received rosuvastatin, an observation also reported in the 4D study. A post hoc analysis of the 731 diabetic patients receiving hemodialysis reported a 32% risk reduction of composite primary endpoints among patient with diabetes on hemodialysis in the treated arm (HR 0.68, 95% CI 0.51–0.90) [277].

There were three randomized trials that examined the effect of fibrates relative to placebo in patients with diabetes and CKD. The Veterans Affairs High-density lipoprotein Intervention Trial (VA-HIT) [278] found evidence that gemfibrozil reduces risk of major cardiovascular events (fatal coronary heart disease, nonfatal MI, and stroke) by 42% compared with placebo (RR 0.58, 95% CI 0.38–0.89) in a post hoc analysis of 297 individuals with low eGFR (GFR <75 ml/min/1.73 m^2) and diabetes. The Diabetes Atherosclerosis

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Intervention Study (DAIS) [279] and the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study [280, 281] reported that fenofibrate treatment significantly lowered the risk of developing new onset of moderately increased urine protein compared with placebo (RR 0.87 in patients with type 2 DM, 95% CI 0.77–0.97). Fenofibrate also promoted regression from moderately increased urine protein to normoalbuminuria (RR 1.15, 95% CI 1.04–1.28, $n = 2260$, two trials), but did not change the risk of progression from moderately to severely increased urine protein (RR 1.07, 95% CI 0.43–2.63, one trial, $n = 97$).

Placebo-controlled trials evaluating the addition of the PCSK9 inhibitors evolocumab and alirocumab to maximally tolerated doses of statin therapy in participants who were at high risk for atheroscletoric CVD demonstrated an average reduction in LDL cholesterol of 36–59%. These agents can be considered as adjunctive therapy for patients with diabetes at high risk for or who require but are intolerant to high-intensity statin therapy [282, 283]. The effects of this class of agents on CVD outcomes in patients with CKD remain unknown.

Antiplatelet Agents

The use of antiplatelet and antithrombotic agents in patients with DKD or CKD for prevention of CVD has not been robustly studied. The Antithrombotic Trialists' (ATT) collaborators conducted a patient-level meta-analysis of the six large trials of aspirin for primary prevention in the general population. These trials included 95 000 participants, including almost 4000 with diabetes. The study found aspirin reduced the risk of serious vascular events by 12% (RR 0.88, 95% CI 0.82–0.94), and the largest reduction was for nonfatal MI, with little effect on CVD death (RR 0.95, 95% CI 0.78–1.15) or total stroke [284]. A post hoc analysis of the HOT trial indicated net benefit for prevention of CV events for aspirin in patients with CKD and high BP, but predominantly included patients with relatively mild CKD [248]. Evidence supports use of either ticagrelor or clopidogrel in combination with aspirin for at least 1 year in patients following an ACS if no percutaneous coronary intervention was performed, and clopidogrel, ticagrelor, or prasugrel if a percutaneous coronary intervention was performed [285]. In patients with diabetes and prior myocardial infarction, adding ticagrelor to aspirin significantly reduces the risk of recurrent ischemic events, including cardiovascular and coronary heart disease death [286]. Post hoc analyses of trials of other antiplatelet agents have raised questions of whether the balance of benefit and harm is the same in patients with diabetes and/or CKD [287] and whether some agents may be more effective in CKD than others [288]. These results need to be interpreted with caution, as most participants with CKD had mild CKD. There are potential harms associated with antiplatelet/antithrombotic agents. Given the very high rates of thrombotic and embolic events (venous and arterial), particularly in advanced CKD, more studies are needed to investigate the longer-term benefits of these therapies in diabetes with CKD.

Promising Biomarkers in Predicting Risk of DKD

Not all patients with albuminuria progress to kidney failure or CVD, and the same is true of many patients with impaired kidney function (eGFR $<60\,\text{ml/min/1.73\,m}^2$), therefore an intensive search for novel biomarkers in blood or urine that could improve diagnostic and prognostic precision in early or later stages of DKD has been ongoing during the past decades.

In a longitudinal cohort study of 410 patients with type 2 DM with 12 years of follow-up, 59 patients developed kidney failure and 84 patients died without kidney failure. Baseline circulating tumor necrosis factor receptor (TNFR1) and TNFR2 were associated with risk for kidney failure. The cumulative incidence of kidney failure for patients in the highest TNFR1 quartile was 54% after 12 years but only 3% for the other quartiles ($P < 0.001$). In Cox proportional hazard analyses, TNFR1 predicted risk for kidney failure in both proteinuric and nonproteinuric groups [289]. Similar findings were reported in a cohort of American Indians with type 2 DM in which elevated serum concentrations of TNFR1 or TNFR2 were associated with increased risk of kidney failure after accounting for traditional risk factors including uACR and eGFR [290].

Using propensity scoring methodology the ADVANCE cohort was divided into those who developed major kidney endpoints ($n = 102$) compared to the control ($n = 179$). This subsidiary analysis showed the baseline total and active TGF-β1 were substantially increased, and bone morphogenetic protein 7 (bone morphogenetic factor (BMP)-7) levels decreased in people with type 2 DM who subsequently developed kidney endpoints compared to matched controls, despite relatively normal baseline kidney function in both groups. The c-statistic was 0.94 for circulating BMP-7 combined with total and active TGF-β1 compared to that of eGFR and uACR combined (c-statistic of 0.73) [291]. Hara et al. have shown that anti-erythropoietin receptor (EPOR) antibodies were found to be a promising marker in 112 Japanese patients with type 2 DM with CKD with a mean follow-up period of 45 months. The event-free rate of kidney events (defined as kidney failure requiring dialysis) in the patients with antibodies was significantly lower than in those without. The presence of EPOR antibodies confers an HR of 2.78 of kidney failure in individuals with DKD [292]. Promising, large, prospective validation cohort

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studies conducted in conjunction with clinical trial to confirm the potential clinical use of these circulating biomarkers is required before routine testing can be recommended in clinical practice.

Novel Interventions Under Current or Recent Investigation in DKD

Given the escalating numbers of patients with DKD, new therapies are constantly in development. A snapshot of treatments in early and late phase trials is shown in Table 24.11; however, results are not yet available.

Conclusion

The growing global burden of DKD needs urgent attention to identify novel treatment strategies to prevent progressive kidney failure and its complications. Several proven treatments supported by evidence are available, but the gap in delaying the progression of DKD warrants discovery of novel therapies. The diagnosis of DKD, which traditionally relies on measuring and monitoring of uACR and kidney function in combination with clinical assessment, may not identify individuals at risk of progressive kidney disease. New markers are constantly being evaluated to improve diagnostic and prognostic precision, but validated evidence for their use is lacking. The discovery, development of an evidence base, and then implementation of new therapeutic agents is necessary for patients with DKD, and will benefit affected individuals, their families, and the community.

Table 24.11 Novel therapeutics being trialed in DKD.

Aldosterone receptor antagonist		Phase 2 study completed
Bardoxolone methyl	TSUBAKI Study	Phase 2 study recruiting
	BEACON	Phase 3 study terminated due to safety concerns
C–C chemokine receptor type 2 (CCR2) antagonism		Phase 2 study completed
Dapagliflozin		Phase 4 study recruiting
Endothelin-A antagonist atrasentan		Phase 3 ceased due to futility
Exenatide		Phase 4 study active but not recruiting
Mineralocorticoid receptor antagonist/finerenone		Phase 2 study completed and Phase 3 underway
		Phase 3 study recruiting
Nox1/4 inhibitor (oral GKT137831)		Phase 2 study completed: negative results in type 2 DM@ with DKD#
		Now being studied in type 1 DM with DKD
Phosphodiesterase 5 inhibitor		Phase 2 study completed
Pirfenidone		Phase 3 study recruiting
Pyridorin		Phase 3 study terminated due to lack of funding

Nox1/4 inhibitor: NADPH oxidase Nox 1 and Nox 4 inhibitor
DM: diabetes mellitus
DKD: diabetic kidney disease

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Lupus Nephritis

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Introduction

Lupus nephritis is an important manifestation of the multisystem autoimmune disease systemic lupus erythematosus (SLE) with clinical features ranging from asymptomatic abnormalities on urine microscopy, to the nephrotic syndrome, to rapid loss of kidney function. It is important to frame the current evidence base for the treatment of lupus nephritis into some historical context (Figure 25.1). It is nearly half a century since the first randomized controlled trial (RCT) in lupus nephritis was published, and this period can be divided into three eras based on the standard of care at the time: steroid alone, steroid plus cytotoxic then steroid plus mycophenolate. The first histological classifications developed because percutaneous kidney biopsy enabled analysis of histology in life rather than at autopsy. Every decade since has seen developments and refinements to the way the disease is classified histologically and thus reported to clinicians by pathologists. Before end-stage kidney disease (ESKD) programs became widely available, many patients with lupus nephritis died from renal failure. With improved immunosuppressive therapies, fewer patients now progress to ESKD and the lower mortality in the modern era may also be attributed to improvements in supportive care with renin-angiotensin system inhibitors to reduce blood pressure and proteinuria, increased use of hydroxychloroquine, better management of complications of treatment such as infection, and better management of cardiovascular risk factors. This chapter presents the current treatment for lupus nephritis and the evidence base behind it (Table 25.1).

Definition

Lupus nephritis is the term for kidney involvement in patients with SLE and is defined by clinical features, laboratory abnormalities, and the histological findings on kidney biopsy. Because SLE involves multiple systems, the disease is best defined by diagnostic criteria such as the American College of Rheumatology (ACR) [1,2] or the Systemic Lupus International Collaborative Clinics (SLICC) [3] criteria (Table 25.2). Lupus nephritis is also heterogeneous and is best defined by a specific histological classification, the International Society of Nephrology (ISN) Renal Pathology Society (RPS) Classification (Table 25.3) [4,5].

Epidemiology

SLE predominantly affects young females from non-Caucasian populations, particularly African Americans. The female: male ratio is 9 : 1 [6]. Three SLE surveillance programs in different United States populations reported almost 4000 prevalent cases of SLE and 752 incident cases between them over a 3-year period [7–9]. The prevalence per 100 000 population using the ACR criteria in African American, Hispanic, Asian, and Caucasian females ranged from 182 to 477, 58 to 179, 50 to 165, and 73 to 122, respectively. The corresponding figures in males were 18–59, 12–22, 5–25, and 5–11, respectively. Prevalence data are lacking in African, subcontinental, and South Asian cohorts [10].

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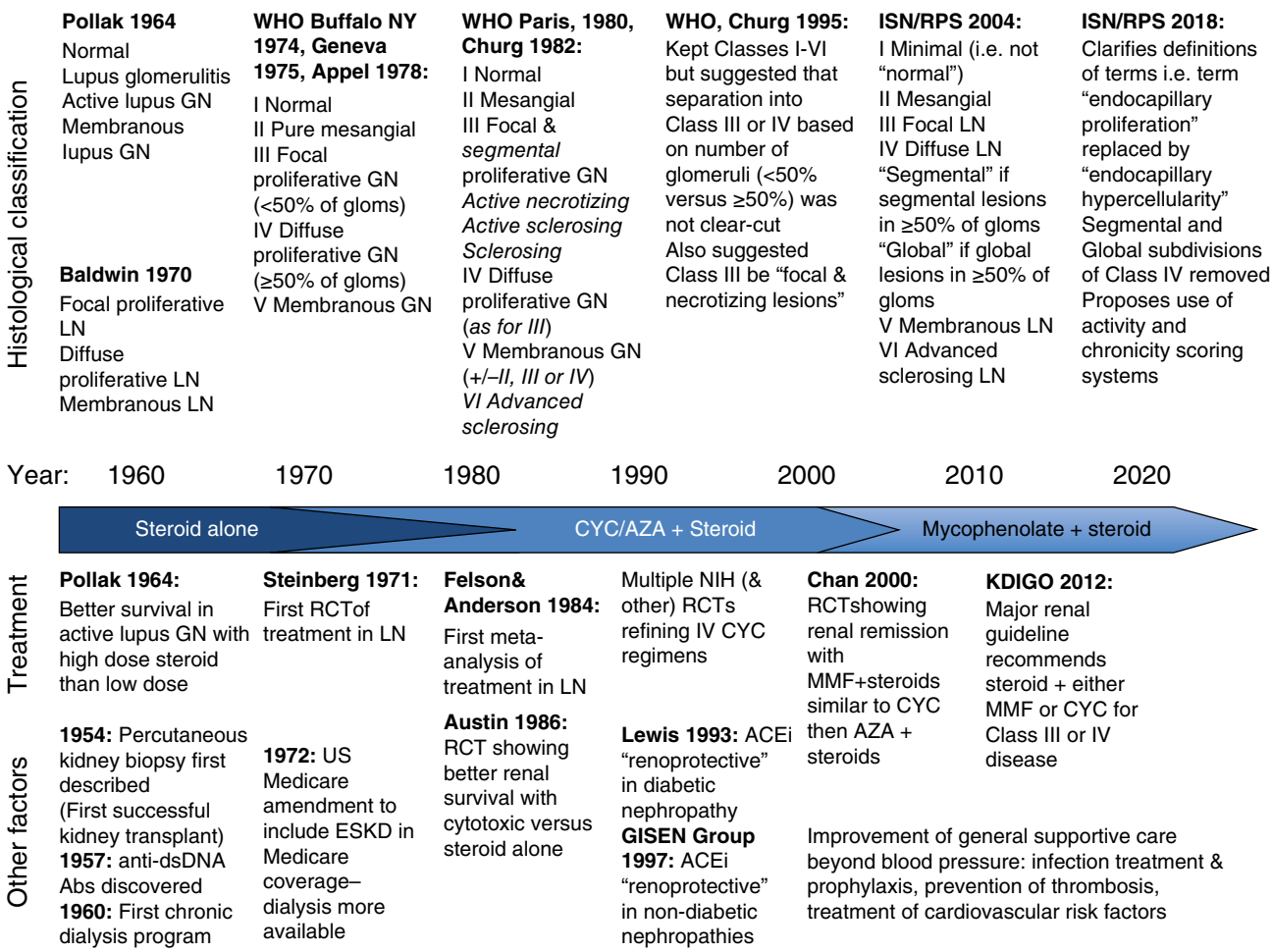

Figure 25.1 Historical perspective of lupus nephritis. CYC, cyclophosphamide; AZA, azathioprine; GN, glomerulonephritis; LN, lupus nephritis; WHO, World Health Organization; ISN/RPS, International Society of Nephrology/Renal Pathology Society; RCT, randomized controlled trial; ESKD, end-stage kidney disease; NIH, US National Institutes of Health; ACEi, angiotensin converting enzyme inhibitor; GISEN, Gruppo Italiano di Studi Epidemiologici in Nefrologia; MMF, mycophenolate mofetil; KDIGO, Kidney Disease Improving Global Outcomes Guideline.

An international inception cohort of 1826 patients with SLE reported that 38.3% of people with SLE have a "renal disorder" [11]. In the United States surveillance studies [7–9], the proportion with "renal disorder," defined as proteinuria or urinary casts in the ACR criteria, ranged from 32 to 45% and, like SLE itself, was consistently highest in African Americans and lowest in Caucasian Americans. Lupus nephritis may also differ by sex. In a meta-analysis of clinical features by sex, males had greater odds of renal involvement (OR 1.51, 95% CI 1.31–1.75), whereas females were more likely to have skin, joint, and serosal involvement [6].

Pathophysiology

In SLE there is disordered immune regulation leading to loss of self-tolerance, production of autoantibodies, and formation of immune complexes. In lupus nephritis, these immune complexes either deposit in, or form within, the kidney. This leads to complement activation, inflammation, and ultimately the various histopathological lesions and clinical manifestations of lupus nephritis.

Preceding these events is genetic susceptibility. Genetic factors play an important role in SLE and lupus nephritis, and the wide variety of gene loci that increase the risk of SLE and lupus nephritis go some way to explaining the clinical heterogeneity of the disease. Concordance of SLE in monozygotic twins is 24% compared to 2% in dizygotic twins and some specific alleles of the major histocompatibility complex on chromosome 6 are strongly associated [10]. For example, having both HLA-DRB1*03 : 01 and DRB1*15 : 01 alleles conferred greater risk for SLE than being homozygous for one allele in a large genotype association study [11]. In this study, the greater the number of risk polymorphisms, the greater the odds of SLE. In African

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Table 25.1 Treatment for lupus nephritis.

Treatment	Recommendation	Certainty of evidence (relevant outcome measure)	Strength of recommendation
All patient with lupus nephritis			
	We recommend that all patients with lupus nephritis be treated with hydroxycholoroquine.	*Low*	Strong [13–16]
ISN/RPS Class I disease			
	We suggest treatment only for extrarenal manifestations of SLE.	*Very low*	Weak
ISN/RPS Class II disease			
	We suggest treatment only for extrarenal manifestations of SLE. Consider immunosuppressive treatment if substantial proteinuria or evidence of podocytopathy.	*Very low*	Weak
ISN/RPS Class III or IV disease, with or without Class V			
Induction			
Mycophenolate	We suggest mycophenolate (i.e. 3 g per day of mycophenolate mofetil in divided doses) be used for initial treatment of lupus nephritis Class III or IV because it is equivalent in inducing remission to cyclophosphamide but has an overall more favorable toxicity profile.	*Low* (complete remission, partial remission) *Moderate* (alopecia with cyclophosphamide, diarrhea with mycophenolate)	Weak [17–18]
Cyclophsophamide	We suggest that intravenous cyclophosphamide (either 0.5–1.0 g/m^2 monthly or 0.5 g fortnightly for six doses) be used as an alternative to mycophenolate to induce remission in lupus nephritis because it is equivalent to mycophenolate. This could be for patients who do not tolerate mycophenolate or whose disease is resistant to mycophenolate.	*Low* (complete remission, partial remission)	Weak [17–18]
Mycophenolate plus tacrolimus	We suggest that mycophenolate mofetil plus tacrolimus be considered as a third alternative as although it was better than intravenous cyclophosphamide at inducing complete remission, results are from a single center with participants largely of Asian ethnicity.	*Low* (complete remission, stable kidney function)	Weak [17–18]

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Corticosteroid	We recommend that corticosteroids be included with the above regimens as they were a component of these regimens in all RCTs. The dose (prednisolone 0.6–1.0 mg/kg/day) and use of intravenous methyprednisolone should be dictated by severity of renal and extrarenal disease and reduced as quickly as possible. It should be noted that major infections were similar in comparison with prednisolone alone with prednisolone plus cytotoxic.	*Moderate* (major infection)	Strong [17]
Maintenance			
Mycophenolate	We recommend mycophenolate be continued as maintenance therapy because treatment results in less renal relapse and doubling of serum creatinine than azathioprine and with a more favorable toxicity profile than azathioprine. Whether and when to withdraw maintenance therapy is not known.	*Moderate* (renal relapse, doubling of serum creatinine) *Low* (leucopenia)	Strong [17–18]
ISN/RPS Class V disease with no proliferative (Class III or IV) disease			
Nonimmunosuppressive	We suggest that all patients with Class V lupus nephritis receive "anti-proteinuria" therapy with blockade of the renin-angiotensin system.	Low	Strong
Immunosuppressive	We suggest that patients with pure Class V lupus nephritis who have nephrotic syndrome or persistent nephrotic range proteinuria can be treated with similar immunosuppression to Class III or IV disease.	Low	Weak [17]
	We suggest that a calcineurin inhibitor could be considered as it was effective in inducing remission in one RCT.	Low	Weak [19]
	We suggest that for patients with Class V lupus nephritis and proteinuria below 3 g/day, the decision to treat with immunosuppression and the choice of immunosuppression be guided by individual patient risk factors.	Low	Weak
ISN/RPS Class VI disease			
	We recommend immunosuppressive therapy not be given to patients with Class VI disease.	*Very low*	Strong

GRADE assessment of the certainty of the evidence [20]: High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different* is low. Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different* is moderate. Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different* is high. Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different* is very high. **Substantially different = a large enough difference that it might affect decision-making*.
ISN/RPS, International Society of Nephrology/Renal Pathology Society; RCT, randomized controlled trial; SLE, systemic lupus erythematosus.

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Table 25.2 Major diagnostic criteria for the diagnosis of SLE.

Organ	ACR criteria [1,2]	SLICC criteria [3]
Skin	Malar rash	Acute cutaneous lupus
	Discoid rash	Chronic cutaneous lupus
	Photosensitivity	
Mucosa	Oral ulcers	Oral ulcers
Hair		Alopecia
Joint	Nonerosive arthritis in ≥2 joints	Synovitis in ≥2 joints
Serosa	Pleuritis or pericarditis	Typical pleurisy or pericardial pain lasting ≥1 day
Kidney	Renal disorder = proteinuria>0.5 g/day or > 3+ on dipstick OR cellular casts of any type	Renal = proteinuria>0.5 g/day or equivalent protein:creatinine ratio OR red blood cell casts
Nervous system	Seizures OR psychosis	Seizures, psychosis, mononeuritis multiplex, myelitis, peripheral or cranial neuropathy, or acute confusion
Hematological	Haemolytic anemia OR leukopenia (<4000/ml twice) OR lympnopenia (<1500/ml twice) OR thrombocytopenia (<100 000/ml)	Haemolytic anemia Leukopenia (<4000/ml once) OR lympnopenia (<1000/ml once) Thrombocytopenia (<100 000/ml)
Immunological	Immunological: positive lupus erythrmatosus cell test OR anti-dsDNA OR anti-Sm antibody OR false-positive syphilis serology	Positive ANA
	Abnormal ANA titer	Elevated anti-dsDNA
		Positive anti-Sm
		Positive anti-phospholipid antibody
		Low complement
		Direct coombs test

ACR, American College of Rheumatology; ANA, antibodies directed against nuclear components; anti-dsDNA, anti-double-stranded DNA; SLE, systemic lupus erythematosus; SLICC Systemic Lupus International Collaborative Clinics.

American patients, the coding alleles G1 and G2 of the APOL1 gene are strongly associated with nondiabetic kidney disease. In lupus nephritis, the presence of two APOL1 gene risk alleles increased the odds of developing ESKD 2- to 3-fold, and development of ESKD occurred 2 years earlier than in people without two risk alleles [21].

After genetic susceptibility, the next event in developing SLE is the loss of immune tolerance to endogenous nuclear material with autovaccination leading to production of antinuclear antibodies [22]. When cells die, the presence of nuclear material in the extracellular space is minimized by apoptotic cell death or phagocytic clearance. If the methylation state of nuclear material is altered, a failure to recognize the nuclear material as "self" and, worse, interpreting the material to be viral nucleic acid by Toll-like receptors on antigen presenting cells, leads to immune activation by various mechanisms and production of autoantibodies such as anti-double-stranded DNA (anti-dsDNA) [23]. Some of these mechanisms, such as B lymphocyte stimulator (Blys or B-cell activating factor "BAFF"), A Proliferating Inducing Ligand (APRIL) and co-stimulatory molecules are targets of novel therapies (Figure 25.2) [22].

This immune activation and proliferation of autoreactive T and B cell populations leads to production of various antibodies directed against nuclear material, including anti-dsDNA. Although clearly important to measure clinically and pathogenic in experimental models, the precise role anti-dsDNA antibodies play in lupus nephritis is still being elucidated. Binding directly to cross-reactive antigens such as annexin II or indirectly to chromatin material that deposits in the kidney leads to effects such as cell proliferation and recruitment of inflammatory cells [24].

The variable pattern of immune complex deposition contributes to the diversity of histological lesions in lupus nephritis. Immune complex deposition or formation restricted to the mesangium generally leads to milder disease (ISPN/RPS Class I and II), immune complexes in the subendothelial space causes the most kidney-threatening forms of lupus nephritis (ISPN/RPS Class III and IV), and

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Table 25.3 The ISN/RPS classification of lupus nephritis with 2018 clarifications.

Class	Description	Detailed description	ISN/RPS 2018 Clarifications
I	Normal	Normal by light microscopy (LM), mesangial immune deposits may be present on immunofluorescence (IF) or electron microscopy (EM)	
II	Mesangial disease	Mesangial hypercellularity; subepithelial or subendothelial immune deposits not visible by LM, but may be evident on IF or EM	Mesangial hypercellularity defined as ≥4 mesangial cell nuclei surrounded by matrix and away from the hilum
III	Focal lupus nephritis	Focal (<50% of glomeruli) segmental or global disease; lesions may include: • endocapillary hypercellularity • subendothelial immune deposits visible on LM as "wire loop" lesions • adhesions • fibrinoid necrosis • crescents	The term "endocapillary hypercellularity" replaces the term "endocapillary proliferation" as cells other than endothelial cells may be present. Adhesions, fibrinoid necrosis specifically defined Definition of crescent changed to extracapillary hypercellularity involving ≥10% (*not 25%*) of the circumference of Bowman's capsule; cellular, fibrocellular and fibrous crescents defined by proportion of fibrous and cellular elements New classification recommends *not* using the categories of global (G) and segmental (S), and not using terms for active (A), chronic (C) and active and chronic (A/C) lesions; rather, a semiquantitative scoring system is suggested
IV	Diffuse lupus nephritis (sometimes referred to as "diffuse proliferative lupus nephritis")	Diffuse (≥50% of glomeruli) segmental or global disease; lesions as per Class III but more widespread; features of membranoproliferative (mesangiocapillary) pattern may be present	Clarifications as per Class III
V	Membranous lupus nephritis	Subepithelial immune deposits in a typical membranous pattern; there may be mesangial deposits and hypercellularity May be present with focal (Class V + III) or diffuse (Class V + IV) disease	
VI	Advanced sclerosing lupus nephritis	Global glomerulosclerosis in ≥90% of glomeruli	Likely to be removed in future classifications as rarely seen

ISN/RPS, International Society of Nephrology/Renal Pathology Society.

subepithelial immune complexes cause membranous disease (ISPN/RPS Class V). This binding to intrarenal autoantigens results in complement activation, activation of Fc receptors, recruitment of inflammatory cells, and tissue inflammation [23]. Untreated, this inflammation leads to tissue damage, fibrosis, and loss of kidney function.

Diagnosis

The diagnosis of lupus nephritis ultimately rests on the kidney biopsy and histological classification of the lesion. Because the histological classification is pertinent to subsequent discussion, this will be described first.

Histological Classification of Lupus Nephritis

The current histological classification of lupus nephritis has been developed over many decades and continues to evolve (Figure 25.1 and Table 25.3) [4,5]. These classifications formed an important component of the inclusion criteria for the RCTs that provide the evidence base for treatment of lupus nephritis and an appreciation of their evolution over time is important. The earliest classification of the glomerular lesions in SLE was published in 1964 by Pollak et al. [25], who analyzed kidney tissue from 176 biopsy and necropsy specimens collected between 1953 and 1962 to study the natural history of the disease. They classified what they saw under the microscope as normal, lupus glomerulits with "mild local and focal changes in the glomerular tuft," active

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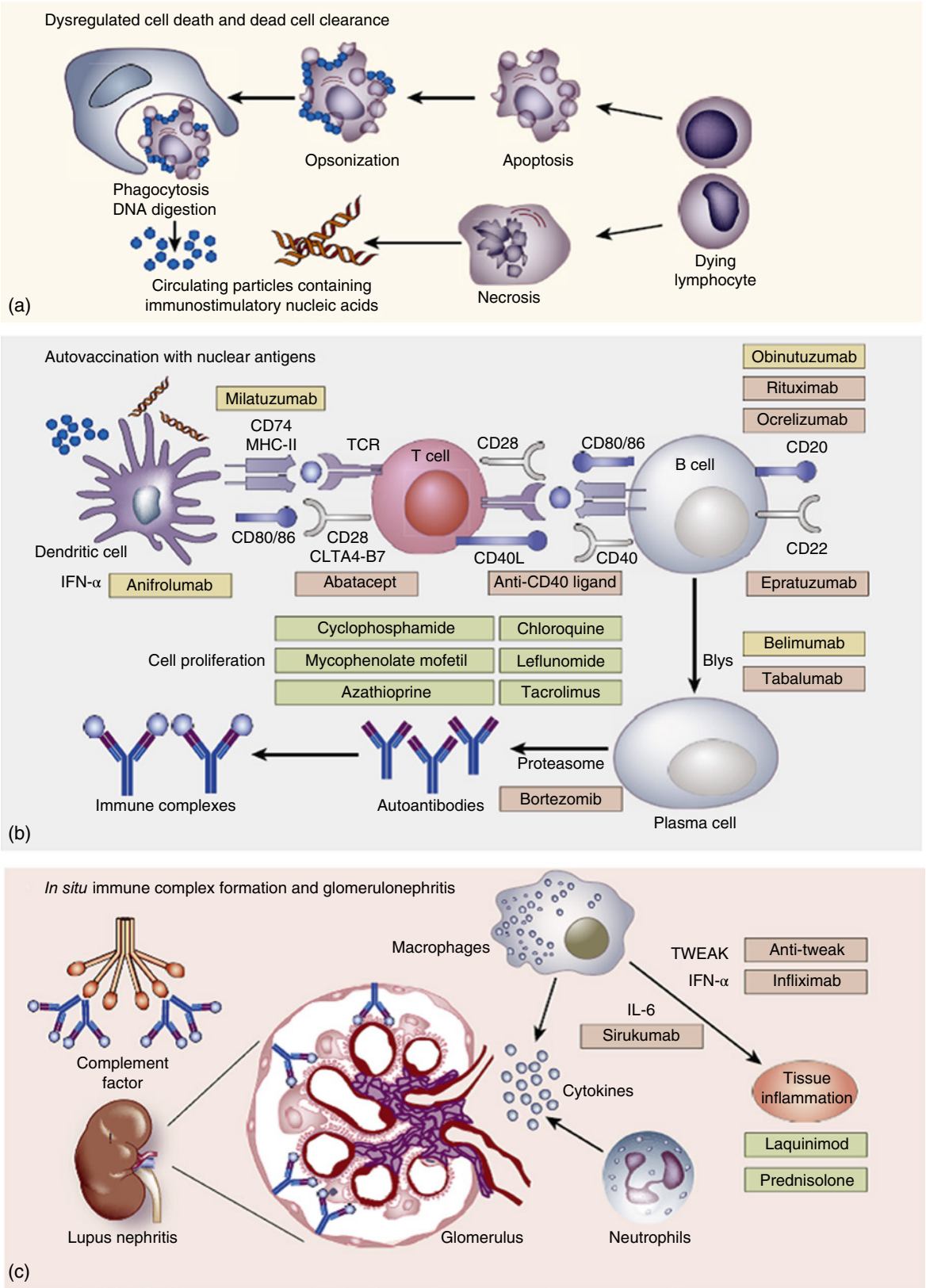

Figure 25.2 Pathogenesis of lupus nephritis. Dysregulated cell death (a) leads to development of autoantibodies (b) and ultimately immune complexes that result in kidney injury. The site of action of established and novel treatments is indicated. result in kidney injury (c). *Source:* Courtesy of Anders & Rovin [23]. © 2016, Elsevier.

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lupus glomerulonephritis with "a more severe proliferative and membranous process, frequently associated with necrotizing features," or membranous lupus glomerulonephritis with "diffuse thickening of the glomerular basement membrane." Baldwin et al. published a similar study in 1970 and used the terms "focal proliferative lupus nephritis" and "diffuse proliferative lupus nephritis" in place of "lupus glomerulitis" and "active lupus glomerulonephritis," respectively [26]. The first World Health Organization (WHO) classification was formulated at conferences in Buffalo, New York in 1974 and Geneva, Switzerland in 1975 but did not appear in peer-reviewed literature until 1978, when it was used "with minor changes" in a study reporting the clinical course of 56 patients over time [27]. This classification introduced mesangial lesions as a distinct entity. Advanced sclerosing glomerulonephritis was added at the International Study of Kidney Diseases in Children Meeting in Paris in 1980 and this classification was published in Churg's *Renal Disease: Classification and Atlas of Glomerular Diseases* [28]. Further revisions were made in 1995 and published in the second edition of that textbook [29]. Along the way, debate about the distinction between Class III and Class IV disease, and definitions of terms such as "proliferative" has continued. A Consensus Conference at which the ISN and RPS combined to refine this classification took place at Columbia University, New York in 2002 [4] and this ISN/RPS classification, which is now in widespread use (Table 25.3) continues to be refined in order to improve clarity and reproducibility [5].

Patients who have been recruited into RCTs of therapy have generally had a kidney biopsy demonstrating ISN/RPS Class III, IV, and/or V lupus nephritis, or equivalent in older classifications, and had to meet the ACR or SLICC criteria for a diagnosis of SLE. In clinical practice it is possible to have lupus nephritis diagnosed on kidney biopsy without strictly meeting all of the clinical criteria.

Clinical Presentations of Lupus Nephritis

The kidney is but one organ involved in SLE, a chronic condition that relapses and remits over time. Thus, lupus nephritis can be the first presentation of SLE, can occur in someone with a known diagnosis of SLE, or can recur in someone with SLE who has previously had lupus nephritis. Given the epidemiology of lupus nephritis, young non-Caucasian females presenting with features of glomerular disease such as nephrotic syndrome should have lupus nephritis high on the list of differential diagnoses, even in the absence of known SLE. The presence of systemic symptoms such as fever or weight loss, musculoskeletal, serosal or skin features should raise that clinical suspicion even higher. Clinical features of SLE are variable and involve multiple systems. Two diagnostic criteria (Table 25.2) are widely used to help clinicians make a diagnosis of SLE and report sensitivity and specificity for a diagnosis of SLE to be greater than 90% [3].

The "renal disorder" criteria in both classifications are based on urinary findings: a measure of proteinuria and the presence of red blood cells or casts in the urine. In a predominantly Caucasian population of 499 patients with lupus nephritis, 35% presented with urinary abnormalities such as hematuria or proteinuria, 35% presented with nephrotic syndrome, 18% presented with nephritic syndrome, and 6% had rapidly progressive renal failure [30]. Over time, the proportion with nephrotic syndrome has remained stable and the more severe clinical presentations declined (Figure 25.3).

The work-up of a patient with suspected lupus nephritis, whether or not they have known SLE, takes into account clinical symptoms, assessment of glomerular disease activity, and serological abnormalities. Glomerular disease activity is assessed with urine microscopy for evidence of glomerular bleeding such as dysmorphic red blood cells and casts, assessment of urine protein excretion, and measurement of kidney function. Serological testing in lupus includes measurement of complement activity, with C3 and C4 being the most widely available tests, antibodies directed against nuclear components (ANA), which are sensitive but not specific for lupus, and anti-dsDNA antibodies, which are more specific for lupus. Other evaluations might include general measures of inflammation such as erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) and evaluation of extracted nuclear antigens (ENA), which include various antibodies associated with specific SLE manifestations. A person with lupus nephritis will typically have positive ANA, depressed levels of complement components C3 and C4, and raised anti-dsDNA.

Because of the high prevalence of kidney disease in SLE, careful periodic assessment of kidney function and glomerular disease activity as described above is also part of the ongoing management of patients with SLE. Patients who have been diagnosed with or treated for lupus nephritis require close monitoring of these parameters and a fall in C3 and C4 and a rise in anti-dsDNA may precede onset of significant kidney disease.

Importantly, definitions of renal remission and renal relapse in clinical trials are based on the glomerular disease features, particularly proteinuria. Although there is no consensus for the definition of remission in lupus nephritis [14], a common definition of complete remission following induction therapy is the return of serum creatinine to normal, urinary protein excretion to less than 0.5 g/day, and an inactive urinary sediment. This was used

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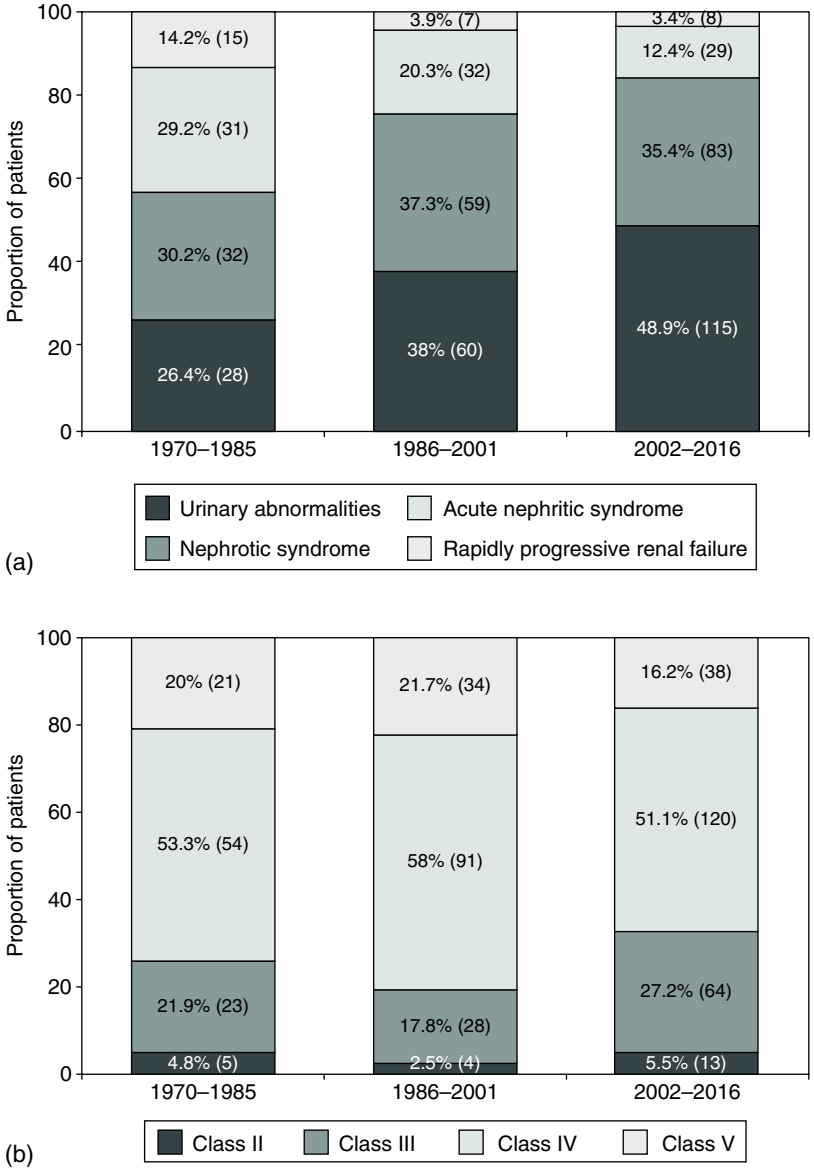

Figure 25.3 Distribution of (a) clinical features of lupus nephritis and (b) histological classification of lupus nephritis a single center across three eras. *Source:* Courtesy of Moroni et al. [30]. © 2018, BMJ Publishing Group Ltd.

in the 2018 Cochrane review update [17]. A common definition of partial remission is a fall in proteinuria to less than 3.0 g/day if baseline proteinuria was greater than 3.0 g/day, or a greater than 50% reduction if baseline proteinuria was less than 3.0 g/day in addition to stabilization of serum creatinine to within 25% of baseline, as used in the induction phase of the Aspreva Lupus Management Study (ALMS) Group study [31]. Renal relapse, or "flare," in clinical trials is defined variously as an increase in proteinuria and/or creatinine. For example, in the maintenance phase of the ALMS study, this required a doubling of urinary protein:creatinine ratio from the end of induction with proteinuria above either 1 or 2 g/day depending on whether the postinduction value was above or below 0.5 g/day [32].

Role and Interpretation of the Kidney Biopsy in Lupus Nephritis

A kidney biopsy is critical to making a diagnosis of lupus nephritis and determining treatment. The indications for performing a kidney biopsy in SLE are not dissimilar to non-SLE presentations. Presentations with the nephrotic syndrome, nephritic syndrome, and/or rapidly progressive kidney failure warrant a kidney biopsy. Hematuria and/or non-nephrotic proteinuria in patients with SLE are also strong reasons to consider a kidney biopsy, particularly proteinuria of 0.5 g/day or greater. Because clinical features don't always match histological features, a lower threshold should be applied to the decision to perform a kidney biopsy in patients with SLE. The potential risks of

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the procedure should be weighed against the potential benefits of a kidney biopsy in each clinical situation. The benefits of a kidney biopsy in patients with suspected lupus nephritis include (i) the appropriate classification of the renal lesion to enable an appropriate level of immunosuppressive therapy (i.e. pure membranous versus membranous with proliferative lesions), (ii) identification of alternative diagnoses or other renal pathology, including thrombotic microangiopathy in antiphospholipid syndrome, and (iii) assessment of tubule-interstitial damage that is important for prognosis [33]. On occasions, one might consider treating a patient with a severe clinical presentation (i.e. overt nephrotic syndrome) and clinical and laboratory features of SLE without a kidney biopsy. However, the arguments in favor of kidney biopsy are sufficiently strong in most cases. Furthermore, because lupus nephritis is a disease that remits with treatment but can relapse over time, many patients with lupus nephritis have multiple kidney biopsies over the course of their disease.

After the biopsy is performed, the clinician should review the histology face to face with the renal pathologist to marry the clinical, laboratory, and histological features of each patient. It is insufficient to just determine which "Class" of lupus nephritis one is dealing with. Face-to-face review enables discussion of the adequacy of the biopsy upon which therapeutic decisions with important consequences are being made. Given the classification relies on the proportions of glomeruli involved, at least 10 glomeruli should be available for light microscopic examination [4], but preferably more. Immunofluorescence for immunoglobulin and complement components is also essential as lupus nephritis usually has extensive immune deposition, particularly of IgG, C3, and C1q, and lack of immune deposition should prompt consideration of other diagnoses. Activity and chronicity have been designated "A," "C" or "A/C" in older histological classifications of lupus nephritis but the most recent report recommends an activity and chronicity scoring system rather than these designations [5]. Such a scoring system is based on that derived by National Institutes of Health (NIH) investigators where a score of 0, 1, 2, or 3 was applied to histological features of activity such as glomerular cell proliferation, leukocyte exudation, karryorrhexis, fibrinoid necrosis, cellular crescents, hyaline deposits, and interstitial inflammation [34]. A similar score was applied to features of chronicity: glomerular sclerosis, fibrous crescents, tubular atrophy, and interstitial fibrosis. This report assessed this semiquantitative scoring against outcome and reported that the combination of tubular atrophy, glomerular sclerosis, and cellular crescents portended the poorest renal outcomes. A modified version of this scoring system has been proposed for further assessment in the latest ISN/RPS report [5]. This report also recommended against the terms "global" and "segmental" that were introduced with the 2002 Classification as their clinical significance was uncertain.

Prognosis

The natural history of lupus nephritis was described in the first description of the different histological appearances by Pollak [25]. After up to 8 years of follow-up, eight of 10 patients with normal kidney biopsy survived, 17 of 23 with lupus glomerulitis survived, 15 of 47 with active lupus glomerulonephritis survived, and all seven patients with membranous glomerulonephritis survived. Twenty-six of the deaths in the active lupus glomerulonephritis group were attributed to renal failure. Similarly, in one of the earlier RCTs for lupus nephritis [35], 50 patients were enrolled, 23 died, and 15 deaths were attributed as "renal death." Only one of the 15 "renal deaths" received renal replacement therapy, the rest dying of renal failure at an average age of just over 20 years.

The efficacy of modern therapy, including modern supportive care, is demonstrated by the improvements in 5-year survival of Class IV lupus nephritis over the decades from 17% in the 1950s and 1960s to 55%, 80%, and 82% in the decades that followed [36]. In 499 patients with lupus nephritis referred to Italian referral centers from 1970 to 2016, 19.8%, 5.9%, and 3.6% died in the periods 1970–1985, 1986–2001, and 2002–2016, respectively. Corresponding figures for ESKD were 24.8%, 9.1%, and 1.3% [30]. In the international inception cohort of the SLICC investigators recruited between 1999 and 2012, 700 of 1827 were considered to have lupus nephritis though only 395 had a kidney biopsy [11]. This showed predominantly Class III (26.8%), Class IV (43.2%), and Class V (31.8%) disease. In patients with lupus nephritis, the 10 year cumulative incidence of ESKD was 10.1% (95% CI 6.6–13.6%) compared to 0.5% in those without lupus nephritis. The 10-year cumulative incidence of death was 5.0% (95% CI 2.3–7.6%) with lupus nephritis and 3.6% (95% CI 0.9–6.2%) without.

Treatment

Lupus nephritis is a classic autoimmune condition that requires giving enough immunosuppression to treat the disease adequately, but not enough to cause harm. The goals of treatment are (i) to induce remission and relieve symptoms of nephrotic syndrome and (ii) to preserve kidney function in the long term. The first goal is relatively straightforward to assess in RCTs (although definitions of

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remission may vary) but the second goal requires very long-term follow-up of relatively infrequent outcomes. The challenge is to simultaneously achieve both of these goals and minimize toxicity of therapy.

Who to Treat

As stated, treatment decisions should be made after careful review of the clinical data and kidney biopsy. In general, ISN/RPS Class I lesions have a good prognosis and do not require specific therapy apart from what is required to treat extrarenal manifestations of SLE. For Class II disease, the minority in biopsy studies, the risk of progressing to more kidney-threatening lesions is difficult to determine. Published reports have few patients, and those that are biopsied again are biopsied for a worsening clinical presentation. Of 19 patients from Hong Kong whose initial biopsy demonstrated Class II lupus nephritis (5% of lupus nephritis biopsies at that institution), 10 required a second biopsy a median of 33 months (range 7–109) after the first [37]. Of these, nine demonstrated more severe disease on the second biopsy (Class III 2, Class IV 5, Class V 2). Similarly, of 41 Argentinian patients who had an initial biopsy with Class II lupus nephritis, 18 had a second biopsy a median of 40 months (range 11–120) later for clinical flares and 17 demonstrated more severe disease (Class III 4, Class IV 10, Class V 3) [38]. The Kidney Disease Improving Global Outcomes (KDIGO) Guidelines [39] suggest treatment directed only at extrarenal manifestations of SLE if proteinuria is less than 1 g/day and immunosuppressive therapy as for minimal change disease if proteinuria is more than 3 g/day (graded 2D in the GRADE system, the lowest level of evidence). The Joint European League Against Rheumatism and European Renal Association–European Dialysis and Transplant Association (EULAR/ERA-EDTA) Guidelines also suggest no treatment in Class II disease if proteinuria is less than 1 g/day; however, this guideline suggests 0.25–0.5 mg/kg/day of prednisolone if proteinuria is above 1 g/day (with other immunosuppressive therapy if required to taper steroid) [40]. Thus, immunosuppressive therapy in Class II disease may be used where a podocytopathy is considered possible, which emphasizes the importance of a thorough and thoughtful review of the kidney biopsy with the renal pathologist. However, there is no RCT evidence that treating Class II lupus with immunosuppression prevents progression to more severe lupus nephritis (Classes III–V).

The majority of RCTs in lupus nephritis have enrolled patients with Class III, IV, and/or V disease, or equivalent in older classifications [25]. Thus, there is a good evidence base for treating these lesions, which are known to have a much worse prognosis than other lesions. This will be discussed in the following sections with treatment of pure membranous Class V disease considered separately.

Class VI disease is essentially near-ESKD and so immunosuppression is not recommended unless it is required for extrarenal disease. These patients generally require preparation for renal replacement therapy.

Therapies Recommended for all Patients

Nonimmunosuppressive Therapy

As in other forms of glomerulonephritis, non-immunosuppressive therapy for lupus nephritis is intended to reduce proteinuria and control hypertension. Although RCTs assessing the kidney protective effects of renin angiotensin system inhibitors have not been performed specifically in lupus nephritis, these agents delay progression in non-diabetic proteinuric nephropathies [41]. Given that hypertension often requires treatment in lupus nephritis, it is reasonable to extrapolate such data to lupus nephritis and recommend the use of renin-angiotensin system inhibitors.

In addition to hypertension, other cardiovascular risk factors warrant attention as people with SLE are at 2–3-fold greater risk of cardiovascular disease [42] and this risk is greater again in patients with lupus nephritis [43]. Traditional cardiovascular risk factors likely combine with inflammation (particularly interferon pathways) and therapies such as corticosteroids to augment this risk [44, 45]. Again, in the absence of RCTs specifically in people with lupus nephritis, one is left to extrapolate the benefits of lipid-lowering therapy in non-lupus studies. It is noteworthy that systematic reviews have demonstrated the benefit of lipid lowering in women, who make up the majority of SLE patients, as well as men [46], and in people with chronic kidney disease (CKD) [47]. Thus, controlling blood pressure, smoking cessation, and lipid-lowering therapy are important considerations for prevention of cardiovascular disease in the long term.

Supportive therapy also includes prevention of venous thromboembolism in patients who are nephrotic, prophylaxis for opportunistic infections such as *Pneumocystis jirovecii*, prevention and management of corticosteroid-induced osteoporosis, and active management of fertility issues in females and males who may be exposed to large cumulative doses of cyclophosphamide.

Antimalarial Therapy

Antimalarial therapy with hydroxychloroquine is recommended for all patients with lupus nephritis. Although this is not based on high-quality RCTs and systematic reviews, analysis of a mixture of randomized and non-randomized studies suggests that antimalarials are effective at preventing lupus flares and prolonging survival [13,15].

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Antimalarial therapy is widely recommended for the treatment of constitutional symptoms in SLE guidelines [14] and may delay progression to an estimated glomerular filtration rate (eGFR) <60 ml/min [16]. The most concerning adverse effect is retinal toxicity, which is greater with chloroquine than hydroxychloroquine, and the Royal College of Ophthalmologists recommends annual screening for retinopathy after taking hydroxychloroquine for more than 5 years, or earlier if receiving a dose of more than 5 mg/kg/day, renal impairment, or concurrent tamoxifen use [48]. The risk of retinal toxicity is considered low on a dose of 200 mg daily, which is sufficient for most people.

Immunosuppressive Therapy for Class III and IV Disease, Alone or Combined with Class V

Induction Versus Maintenance Therapy

Immunosuppressive therapy aims to induce and maintain disease remission to maximize patient and renal survival. Induction therapy may last for 6 months or more. Important clinical outcomes such as death and ESKD are more difficult to study in RCTs because they require either a very large sample size or very long follow-up. RCTs of induction therapy have been of insufficient follow-up (median 12 months, range 2.5–48 months) and sample size (only three trials have recruited more than 350 participants) to assess these outcomes [17]. Complete remission at 24 weeks is commonly reported and generally defined as proteinuria less than 0.5 g/day with normal (or near normal) serum creatinine and normal urinalysis. Maintenance therapy follows induction therapy and cannot be considered as entirely separate. Studies of maintenance therapy require much longer follow-up and outcomes include doubling of serum creatinine, ESKD, death, and renal flare. The definition of renal flare is dependent on how complete a remission was achieved after induction. Measures comprising the definition of renal flare in one RCT [32] included a doubling of a measure of proteinuria with proteinuria above 1 g/day (or 2 g/day depending on earlier response), a 25% increase in creatinine, and new or increased red blood cells or casts on urine microscopy. Regimens for induction and maintenance therapy are described according to the three major eras of treatment for lupus nephritis (Figure 25.1).

Corticosteroids Alone

The earliest reports of lupus nephritis demonstrated benefit in treating patients with high doses of corticosteroids. For example, the report by Pollack with the first histological classification reported better renal outcomes in active lupus glomerulonephritis with high-dose versus low-dose corticosteroid [25]. Fourteen of 31 patients receiving high-dose corticosteroids survived compared to one of 16 patients receiving low-dose corticosteroids. Although corticosteroids have not been compared to placebo in an RCT, they have remained an integral component of treatment regimens. A common starting dose is 1 mg/kg daily (up to 60 mg/day) with varying rates of tapering. Intravenous methylprednisolone is included in some regimens and may be considered for more severe clinical presentations, such as with crescents on biopsy. Although effective in gaining control of active disease, corticosteroids have substantial metabolic, cosmetic, and other toxicities that influence tolerability and adherence. There is therefore much merit in finding treatment regimens that use minimal corticosteroid doses [49].

Cyclophosphamide or Azathioprine plus Corticosteroids

The benefit of adding cytotoxic therapy to corticosteroids was demonstrated in a pooled analysis of eight trials that included between 13 and 50 participants each [50]. Patients receiving steroid combined with cytotoxic therapy (either cyclophosphamide or azathioprine) were less likely to experience renal deterioration, ESKD or die as a result of their nephritis compared to patients receiving steroids alone. All-cause mortality did not differ. The first large RCT randomized 107 patients between 1969 and 1981 to prednisolone either alone, with azathioprine, with oral cyclophosphamide, with azathioprine plus oral cyclophosphamide, or with intravenous cyclophosphamide [51]. The last two groups were introduced part-way through the trial in 1973. Oral and intravenous cyclophosphamide in combination with corticosteroids was superior to corticosteroids alone in preventing doubling of serum creatinine and ESKD, and oral and intravenous cyclophosphamide exhibited similar efficacy and safety. This was the first of a series of trials performed through the National Institutes of Health in the United States, the so-called "NIH" studies.

The NIH regimen consisted of six 0.5–1.0 g/m^2 doses of intravenous cyclophosphamide every month adjusted according to the white cell count, along with prednisolone 0.5 mg/kg/day. This regimen was then compared to a similar dose of prednisolone plus six infusions of methylprednisolone 1.0 g/m^2 every month (steroid alone), and a third arm in which patients continued to have intravenous cyclophosphamide every 3 months for 2 years after the initial six doses of cyclophosphamide (cyclophosphamide "maintenance") [52]. This RCT recruited 65 patients between 1981 and 1991. Continuing cyclophosphamide as maintenance resulted in fewer exacerbations after the first 6 months, and fewer patients experienced a sustained doubling of serum creatinine in this group than the short course (6 months) of cyclophosphamide group and the steroid alone group (15%

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vs. 35% vs. 48%, respectively). A subsequent study recruited 82 patients between 1986 and 1990 and modified the steroid-alone regimen, continuing monthly doses of methylprednisolone for at least 12 months (maximum 36 doses) [53]. Two intravenous cyclophosphamide arms were similar to the previous study except that one was combined with monthly methylprednisolone. This latter combination therapy group had more renal remission (proteinuria <1 g/day) than the cyclophosphamide alone and methylprednisolone alone groups: 17 of 28 vs. 13 of 27 vs. 7 of 27, respectively. After a median of 11 years of follow-up, the probability of no treatment failure (first occurrence of death, doubling of serum creatinine, or need for off-protocol immunosuppression) was ~70% in the combination group, ~55% in the cyclophosphamide alone group, and ~40% in the methylprednisolone alone group [54]. During follow-up, 17 of 27 patients randomized to methylprednisolone alone received cyclophosphamide and the benefits of these regimens came at a cost: 36% of the combination therapy patients had avascular necrosis, 60% developed amenorrhoea at a median age of 33 years, and 26% experienced herpes zoster infection.

Given the concerns of cumulative cyclophosphamide toxicity, the use of lower dose cyclophosphamide (six fortnightly intravenous cyclophosphamide pulses at a fixed dose of 500 mg, followed by azathioprine as maintenance therapy) was compared to the NIH cyclophosphamide regimen described above in the Euro-Lupus Nephritis Trial (ELNT) [55]. This trial showed low-dose cyclophosphamide was comparable to high-dose cyclophosphamide in inducing disease remission but no statistically different reduction in adverse effects of therapy could be demonstrated.

Azathioprine as induction therapy was tested in the very early trials and although it was compared directly to intravenous cyclophosphamide in Austin's study [51], there was insufficient power because this trial included five treatment groups. A study addressing this issue was performed in The Netherlands and randomized 87 people with lupus nephritis to either intravenous cyclophosphamide as per the NIH regimen for 2 years (but at a fixed dose of 750 mg/m^2) or azathioprine 2 mg/kg/day plus three daily pulses of methylprednisolone 1 g at baseline then 2 and 6 weeks later [56]. Patients randomized to cyclophosphamide received oral prednisolone 1 mg/kg/day initially and patients randomized to azathioprine received oral prednisolone 20 mg/day initially. After a median follow-up of 5.7 years, relapses were significantly more frequent in the azathioprine group, and doubling of serum creatinine was also more frequent but did not reach statistical significance. There was more herpes zoster infection with azathioprine, but other parameters such as kidney function and proteinuria were similar. Azathioprine was used for induction of remission in lupus nephritis less frequently than cyclophosphamide. However, azathioprine was commonly used to maintain remission after induction.

The Cochrane Kidney and Transplant group's first systematic review of lupus nephritis included most of the above studies and demonstrated that cyclophosphamide-based regimens reduced the risk of doubling of serum creatinine (relative risk [RR] 0.59, 95% confidence interval [CI] 0.40–0.88) compared to steroid alone, but did not reduce mortality or ESKD [57]. However, the risk of ovarian toxicity was increased with cyclophosphamide, an important toxicity in a patient group that consists predominantly of women of childbearing age. Major infections and herpes zoster infections did not occur more frequently with cytotoxic therapy than with steroids alone.

Mycophenolate Mofetil plus Corticosteroids

In 2000, Chan et al. published a RCT of 42 patients from Hong Kong with WHO Class IV lupus nephritis [58]. They compared mycophenolate mofetil 1 g twice daily and prednisolone 0.8 mg/kg/day for 12 months to oral cyclophosphamide 2.5 mg/kg/day and prednisolone 0.8 mg/kg/day for 6 months then azathioprine 1.5 mg/kg/day and prednisolone for 6 months. Complete remission by 12 months was seen in 17 out of 21 and 16 of 21 patients, respectively. Mycophenolate mofetil thus had similar efficacy, as well as similar infectious complications but no alopecia or amenorrhoea. Given that nephrologists had developed significant experience with mycophenolate in kidney transplant by this stage, it became a viable alternative to cyclophosphamide in lupus nephritis.

Chan's findings were confirmed in a 24-week non-inferiority RCT comparing mycophenolate mofetil to the NIH cyclophosphamide regimen in 140 patients from centers in the United States [59]. Just over half of these participants were African American. Complete and partial remissions occurred in 16 and 21 of 71 patients randomized to mycophenolate mofetil, respectively, and 4 and 17 of 69 randomized to cyclophosphamide, respectively. The difference in complete remissions was significant for "superiority," even though the trial was designed as a noninferiority trial. There were fewer severe infections with mycophenolate mofetil but more patients experienced diarrhea, a known side effect. Subsequently, an international collaboration called the ALMS Study Group (including many United States authors from the aforementioned study) demonstrated in the largest RCT to that time ($n = 370$) that mycophenolate mofetil exhibited similar efficacy in inducing disease remission to intravenous cyclophosphamide (56.2% vs. 53.0%, respectively) [31]. Overall rates of adverse events were similar, although alopecia, nausea, and vomiting

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occurred more often with cyclophosphamide and diarrhea with mycophenolate mofetil. Because it was an international study, there were fewer African American patients but subgroup and post hoc analyses demonstrated that both African American (plus "other") and Hispanic patients had better response rates with mycophenolate mofetil than cyclophosphamide (~60% vs. ~40%). The prespecified interaction between treatment and race was significant ($P = 0.047$).

Importantly, the ALMS Group then randomized the 227 patients who met response criteria at 24 weeks to mycophenolate mofetil 2 g/day or azathioprine 2 mg/kg/day for 36 months [32]. Treatment failure was defined as death, ESKD, doubling of serum creatinine, renal flare or rescue therapy, and occurred in 16.4% of patients receiving mycophenolate mofetil and 32.4% receiving azathioprine. Overall adverse events were common and similar between groups. Prior to this, a RCT comparing quarterly intravenous cyclophosphamide, oral azathioprine, and oral mycohenolate mofetil as maintenance therapy after induction with up to seven monthly doses of intravenous cyclophosphamide demonstrated that the oral azathioprine and mycophenolate mofetil groups had superior event-free survival (events being death or doubling of serum creatinine) to the quarterly intravenous cyclophosphamide [60]. A European study, the MAINTAIN Nephritis Trial, randomized 105 patients to either mycophenolate mofetil or azathioprine at week 12 after all patients received induction with six 500 mg doses of intravenous cyclophosphamide each a fortnight apart [61]. Renal flares occurred in 13 (25%) patients receiving azathioprine and 10 (19%) patients receiving mycophenolate mofetil but there were no significant differences between the groups in any major parameters measured.

The Cochrane Kidney and Transplant Group updated their systematic review in 2012 and this update included the RCTs examining the role of mycophenolate discussed in this section [62]. Mycophenolate mofetil was as effective as intravenous cyclophosphamide for complete remission, stable kidney function, major infection, and mortality, with less ovarian failure (RR 0.15, 0.03–0.80). Used as maintenance therapy, the risk of renal relapse was increased 2-fold with azathioprine compared to mycophenolate mofetil (RR 1.83, 95% CI 1.24–2.71). This systematic review was updated again in 2018 with a total of nine studies (868 participants) comparing mycophenolate mofetil to intravenous cyclophosphamide for induction [17]. The two treatments were equivalent for most outcomes, and findings from this review are used for the Summary of Findings table (Table 25.4). Interestingly, the expected association of more ovarian failure with cyclophosphamide was weakened in this most recent systematic review.

The updated Cochrane review did identify a pilot study ($n = 40$) [63] and larger RCT ($n = 362$) [64] from the same group in China that compared a regimen combining the calcineurin inhibitor tacrolimus 2 mg twice daily with mycophenolate mofetil 500 mg twice daily to intravenous cyclophosphamide 0.75 g/m^2 every month for six doses. Both groups initially received methylprednisolone 500 mg daily for 3 days then prednisolone 0.6 mg/kg. This large RCT demonstrated more complete remission at 24 weeks in the mycophenolate mofetil plus tacrolimus group (45.9%) than the intravenous cyclophosphamide group (25.6%). This promising result has not been replicated and must be interpreted in light of the limited generalizability, being from a homogenous Chinese population, and the influence of the non-immune proteinuria-lowering effect of tacrolimus where a proteinuria-based definition of complete remission was used.

The Current Era: Biologic Therapies

Conventional immunosuppressive therapy with corticosteroids plus either mycophenolate or intravenous cyclophosphamide has considerably improved the outlook for patients with Classes III, IV, or V lupus nephritis, with responses at 24 weeks in one large study of more than 50% with either therapy [31]. However, there remains considerable treatment-related toxicity and room to improve efficacy. As our understanding of the pathophysiology of lupus nephritis evolves, so-called biologic therapies targeted at specific immunological processes (Figure 25.2) have been developed [65]. Results with these agents to date have been suggestive but inconclusive.

Rituximab is a monoclonal antibody that binds specifically to CD20 and depletes autoreactive B cells (but not plasma cells) and reduces autoantibody production [65]. The Lupus Nephritis Assessment with Rituximab (LUNAR) study recruited 144 participants and compared rituximab to placebo when added to standard therapy of mycophenolate mofetil and corticosteroids and demonstrated no difference in clinical outcomes between groups after 12 months [66]. In a post hoc analysis of patients who received rituximab, achieving complete B cell depletion (zero B cells per μl), shorter time to complete B cell depletion, and longer duration of complete B cell depletion were all associated with increased odds of complete response [67]. A rituximab-based regimen has been used at Imperial College London and non-randomized results reported [68]. The purpose of this regimen is to reduce oral corticosteroid use and it consists of rituximab 1 g plus methylprednisolone 500 mg given at days 1 and 15, with mycophenolate mofetil commencing at 500 mg twice daily and titrated up to 1500 mg twice daily (or the maximum tolerated dose). In this series of 50 consecutive

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Table 25.4 Summary of findings: treatment of lupus nephritis.

Outcomes	No. of participants (no. of studies)	Absolute number of patients affected per 1000 patients treated for 1 year (95% CI)	Relative risk (95% CI)	Certainty of the evidence (GRADE)	Conclusion
Intravenous cyclophosphamide versus corticosteroids alone					
All-cause mortality	226 (5)	3 fewer (80 fewer to 139 more)	0.98 (0.53–1.82)	Low ●●○○	Intravenous cyclophosphamide compared to corticosteroids alone may make little or no difference to mortality
End-stage kidney disease	452 (4)	90 fewer (148 fewer–7 more)	0.63 (0.39, 1.03)	Moderate ●●○○	Intravenous cyclophosphamide compared to corticosteroids alone probably decreases end-stage kidney disease
Complete remission in proteinuria	13 (1)	0 (no events in control group)	2.63 (0.13–54.64)	Very low ●○○○	It is uncertain whether mycophenolate mofetil plus tacrolimus compared to intravenous cyclophosphamide makes any difference to complete remission in proteinuria
Doubling of serum creatinine	228 (4)	162 fewer (237–47 fewer)	0.59 (0.40–0.88)	Moderate ●●○○	Intravenous cyclophosphamide compared to corticosteroids alone probably decreases doubling serum creatinine
Renal relapse	84 (2)	337 fewer (403–166 fewer)	0.23 (0.08–0.62)	Moderate ●●○○	Intravenous cyclophosphamide compared to corticosteroids alone probably decreases renal relapse
Stable kidney function	278 (5)	118 more (0–265 fewer)	1.20 (1.00–1.45)	Moderate ●●○○	Intravenous cyclophosphamide compared to corticosteroids alone probably increases stable kidney function
Ovarian failure	147 (3)	222 more (19 fewer–628 more)	2.18 (1.10–4.34)	Low ●●○○	Intravenous cyclophosphamide compared to corticosteroids alone may increase ovarian failure
Major infection	291 (6)	19 fewer (75 fewer–76 more)	0.87 (0.50–1.51)	Moderate ●●○○	Intravenous cyclophosphamide compared to corticosteroids alone probably decreases major infection
Mycophenolate mofetil versus intravenous cyclophosphamide for initial treatment					
All-cause mortality	826 (8)	6 more (19 fewer–51 more)	1.12 (0.61–2.06)	Very low ●○○○	It is uncertain whether mycophenolate mofetil compared to intravenous cyclophosphamide makes any difference to all-cause mortality
End-stage kidney disease	231 (3)	25 fewer (62 fewer–71 more)	0.71 (0.27–1.84)	Very low ●○○○	It is uncertain whether mycophenolate mofetil compared to intravenous cyclophosphamide makes any difference to end-stage kidney disease
Complete remission	868 (8)	38 more (7 fewer–93 more)	1.17 (0.97–1.42)	Low ●●○○	Mycophenolate mofetil compared to intravenous cyclophosphamide may have little or no difference on complete remission
Partial remission	868 (8)	9 more (47 fewer–77 more)	1.02 (0.89–1.18)	Low ●●○○	Mycophenolate mofetil compared to intravenous cyclophosphamide may have little or no difference on partial remission
Ovarian failure	539 (3)	26 more (39 fewer–48 more)	0.36 (0.02–2.18)	Very low ●○○○	It is uncertain whether mycophenolate mofetil compared to intravenous cyclophosphamide makes any difference on ovarian failure
Major infection	699 (5)	2 more (38 fewer–62 more)	1.02 (0.67–1.54)	Low ●●○○	Mycophenolate mofetil compared to intravenous cyclophosphamide may have little or no difference on major infection

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Table 25.4 (Continued)

Outcomes	No. of participants (no. of studies)	Absolute number of patients affected per 1000 patients treated for 1 year (95% CI)	Relative risk (95% CI)	Certainty of the evidence (GRADE)	Conclusion
Leucopenia	753 (6)	81 fewer (133 fewer–16 more)	0.59 (0.33–1.08)	Moderate ●●○○	Mycophenolate mofetil compared to intravenous cyclophosphamide probably decreases leucopenia
Alopecia	622 (3)	170 fewer (194–129 fewer)	0.29 (0.19–0.46)	Moderate ●●○○	Mycophenolate mofetil compared to intravenous cyclophosphamide probably decreases alopecia
Diarrhea	609 (4)	142 more (64–258 more)	2.42 (1.64–3.58)	Moderate ●●○○	Mycophenolate mofetil compared to intravenous cyclophosphamide probably increases diarrhea
Mycophenolate mofetil plus tacrolimus versus intravenous cyclophosphamide for initial treatment					
All-cause mortality	402 (2)	Not estimable	No events	Absent	No events of all-cause mortality occurred in the studies that evaluated mycophenolate mofetil plus tacrolimus compared to intravenous cyclophosphamide
End-stage kidney disease		Not estimable		Absent	No studies comparing low-dose mycophenolate mofetile plus tacrolimus compared to intravenous cyclophosphamide examined end-stage kidney disease
Complete remission	402 (2)	337 more (17–1049 more)	2.38 (1.07–5.3)	Low ●●○○	Mycophenolate mofetil plus tacrolimus compared to intravenous cyclophosphamide may increase complete remission
Partial remission	402 (2)	0 (83 fewer–106 more)	1.00 (0.78–1.28)	Low ●●○○	Mycophenolate mofetil plus tacrolimus compared to intravenous cyclophosphamide may make little to no difference to partial remission
Stable kidney function	402 (2)	222 more (114–358 more)	1.78 (1.40–2.26)	Low ●●○○	Mycophenolate mofetil plus tacrolimus compared to intravenous cyclophosphamide may increase achievement of stable kidney function
Ovarian failure	34 (1)	Not estimable	No events-	Absent	No events of ovarian failure occurred in the studies that evaluated mycophenolate mofetil plus tacrolimus compared to intravenous cyclophosphamide
Major infection	402 (2)	23 more (31 fewer–820 more)	1.65 (0.11–24.44)	Very low ●○○○	It is uncertain whether mycophenolate mofetil plus tacrolimus compared to intravenous cyclophosphamide makes any difference to major infection
Leucopenia	402 (2)	62 fewer (77 fewer–35 more)	0.23 (0.04–1.44)	Very low ●○○○	It is uncertain whether mycophenolate mofetil plus tacrolimus compared to intravenous cyclophosphamide makes any difference to leucopenia
Alopecia	402 (2)	14 fewer (42 fewer–37 more)	0.78 (0.36–1.72)	Very low ●○○○	It is uncertain whether mycophenolate mofetil plus tacrolimus compared to intravenous cyclophosphamide makes any difference to alopecia
Diarrhea	362 (1)	44 more (3 fewer–163 more)	2.33 (0.92–5.94)	Very low ●○○○	It is uncertain whether mycophenolate mofetil plus tacrolimus compared to intravenous cyclophosphamide makes any difference to diarrhea

(Continued)

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Table 25.4 (Continued)

Outcomes	No. of participants (no. of studies)	Absolute number of patients affected per 1000 patients treated for 1 year (95% CI)	Relative risk (95% CI)	Certainty of the evidence (GRADE)	Conclusion
Mycophenolate versus azathioprine to maintain remission after initial treatment					
All-cause mortality	451 (4)	3 fewer (17 fewer–44 more)	0.87 (0.26–2.92)	Very low ●○○○	It is uncertain whether mycophenolate mofetil compared to azathioprine makes any difference to all-cause mortality
End-stage kidney disease	452 (4)	15 fewer (30 fewer–33 more)	0.59 (0.18, 1.92)	Very low ●○○○	It is uncertain if mycophenolate mofetil compared to azathioprine makes any difference to end-stage kidney disease
Renal relapse	452 (4)	114 fewer (162–45 fewer)	0.57 (0.39–0.83)	Moderate ●●●○	Mycophenolate mofetil compared to azathioprine probably decreases renal relapse
Doubling of serum creatinine	452 (4)	46 fewer (68–3 fewer)	0.46 (0.21–0.97)	Moderate ●●●○	Mycophenolate mofetil compared to azathioprine compared to mycophenolate mofetil probably decreases doubling of serum creatinine
Ovarian failure	177 (2)	10 more (24 fewer–161 more)	1.30 (0.29–5.73)	Very low ●○○○	It is uncertain if mycophenolate mofetil compared to azathioprine makes any difference to ovarian failure
Major infection	412 (3)	8 fewer (49 fewer–66 more)	0.92 (0.51–1.67)	Low ●●○○	Mycophenolate mofetil compared to azathioprine may make little or no difference to major infection
Leucopenia	412 (3)	65 fewer (75–32 fewer)	0.18 (0.05–0.6)	Low ●●○○	Mycophenolate mofetil compared to azathioprine may decrease leucopenia
Alopecia	412 (3)	3 more (31 fewer–74 more)	1.05 (0.51–2.15)	Low ●●○○	Mycophenolate mofetil compared to azathioprine may make little to no difference to alopecia
Diarrhea	307 (2)	53 more (61 fewer–318 more)	1.36 (0.58–3.18)	Low ●●○○	Mycophenolate mofetil compared to azathioprine may make little or no difference to diarrhea

CI, confidence interval. Treatment estimates are drawn from a systematic review with network meta-analysis of randomized controlled trials [17, 18]. GRADE assessment of the certainty of the evidence [20]: High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different* is low. Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different* is moderate. Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different* is high. Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different* is very high. **Substantially different = a large enough difference that it might affect decision-making.*
Sources: Tunnicliffe et al. [17, 18] and Hultcrantz et al. [20].

patients, 72% achieved a complete remission at a median of 36 weeks and 90% achieved either complete or partial remission at a median of 37 weeks. Eleven patients relapsed after achieving remission. Oral corticosteroids for more than 2 weeks were only required in two patients who responded and two who did not. Interestingly, 22 of the 50 patients in this report had Class V lupus nephritis. This is relevant because rituximab is increasingly being used for primary membranous glomerulonephritis [69]. This RITUXILUP regimen is the subject of a current RCT (NCT01773616).

Ocrelizumab also selectively depletes CD20+ B cells. In the largest RCT studying lupus nephritis to date, 378 participants were recruited from multiple countries and randomized to placebo, ocrelizumab 400 mg, or ocrelizumab 1000 mg on top of standard care for induction or remission [70]. Standard care, at the discretion of the treating physician, was either mycophenolate mofetil or the ELNT regimen of six fortnightly doses of intravenous cyclophosphamide 500 mg followed by azathioprine 2 mg/kg/day. The primary outcome was response at 48 weeks assessed as either complete, partial, or no response. The trial was

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terminated early because of concerns about an increased frequency of serious opportunistic infections, coupled with the lack of benefit demonstrated in the LUNAR study reported at that time. Opportunistic infections occurred in 0.8% receiving placebo, 3.2% receiving ocrelizumab 400 mg, and 0.8% receiving ocrelizumab 1000 mg. Serious infections were also more frequent in the ocrelizumab 400 mg group and, when stratified by background therapy, more frequent in the patients treated with mycophenolate. This latter subgroup also received more corticosteroid. Because of the early termination, the study outcomes are reported for a modified intention-to-treat group of 223 patients and thus had reduced power. The overall (complete plus partial) renal response rate at 48 weeks was above 50% in all three groups, and the difference in response rate between placebo and the two ocrelizumab groups combined almost reached statistical significance (12.7%, 95% CI −0.8–26.1). The effect appeared greater in the subgroup with ocrelizumab added to the ELNT regimen than when added to mycophenolate mofetil.

Abatacept modulates the CD28-CD80/86 signaling pathway that leads to co-stimulation and T cell activation, and has also been the subject of a large RCT in lupus nephritis [71]. This study compared placebo to two different dosing regimens of abatacept with all patients receiving mycophenolate mofetil and corticosteroids. This trial demonstrated no safety concerns but did not demonstrate a difference in the primary outcome of time to complete response, defined as stable eGFR compared to baseline (within 10%), urine protein:creatinine ratio <30 mg/mmol, and normal urine microscopy on two successive visits (the most stringent definition use in RCTs to date). Using the dataset from this trial, different definitions of complete response from a number of trials as well as that recommended by the ACR [72] were applied [73]. With alternative complete response definitions, the abatacept groups had an estimated difference in complete response of about 15% that was statistically significant. For example, using the ALMS criteria the complete response rates in the placebo, abatacept 10/10 regimen, and abatacept 30/10 regimen were 14, 25, and 30%, respectively, compared to 3, 3, and 5% using the original trial criteria.

Another biologic agent with appealing but not conclusive evidence for benefit in lupus nephritis is belimumab, a monoclonal antibody that inhibits soluble B-lymphocyte stimulator. This agent demonstrated a good response in patients with SLE and thus a post hoc pooled analysis of two trials was performed to assess the renal outcomes [74]. Participants were randomized to two doses of belimumab or placebo on top of standard therapy for active SLE (corticosteroids, hydroxychloroquine). Mycophenolate was used in 10% of the whole cohort ($n = 1684$) and 20% of the 227 patients with renal involvement assessed by the Safety of Estrogens in Lupus Erythematosus National Assessment–SLE Disease Activity Index (SELENA-SLEDAI). Improvement in the renal domain of the SELENA-SLEDAI occurred in 44.6%, 51.1%, and 54.1% of patients receiving placebo, belimumab 1 mg/kg, and belimumab 10 mg/kg, respectively. In the whole cohort, renal flares occurred in 3.0%, 2.5%, and 1.4%, respectively, and the median percentage reduction in proteinuria over 52 weeks was greater in the belimumab groups. However, this agent was not used to treat patients presenting with lupus nephritis and thus should not be extrapolated as a treatment option for such.

Pure Membranous (Class V) Lupus Nephritis

Pure membranous (Class V) lupus nephritis differs from primary membranous glomerulonephritis in that it is associated with an inflammatory disease that relapses and remits, and is less likely than primary membranous glomerulonephritis to remit spontaneously [39]. On the other hand, guidelines suggest similar strategies for treatment [40] such as controlling proteinuria with renin-angiotensin system inhibition if non-nephrotic and reserving immune suppression for more severe (nephrotic) disease. Most of the trials of therapies in lupus nephritis enrolled some patients with Class III, IV, and V disease. In Austin's early trial of 107 patients [51], 16 had pure membranous lupus nephritis and in the more recent ALMS Maintenance Study [32], 35 out of 227 had pure membranous lupus nephritis (more had Class V combined with either Class III or IV). To some degree, it is reasonable to apply the results of these trials to Class V lupus nephritis. There has been little evidence exclusively examining the treatment of class V lupus nephritis. Twenty-three years after his first lupus nephritis RCT, Austin et al. compared the addition of the NIH cyclophosphamide regimen or cyclosporine to prednisone alone in 42 patients with Class V lupus nephritis and nephrotic range proteinuria [19]. Complete remission of proteinuria (to <0.3 g/day) at 1 year occurred in 27% of patients receiving prednisone alone, 60% receiving prednisone plus the NIH cyclophosphamide regimen, and 83% receiving prednisone plus cyclosporine. This supports the use of immunosuppressive agents in patients with nephrotic proteinuria. Treatment for Class V (membranous) lupus nephritis therefore depends on the degree of proteinuria. Patients with proteinuria less than 3.0–3.5 g/day can be treated with renin-angiotensin system blockade to try to reduce proteinuria, just as in primary membranous glomerulonephritis. Other supportive care such as anticoagulation for patients considered at high risk of venous thromboembolism is also important. For patients with "nephrotic" proteinuria above this level, immunosuppression is recommended [39] and this could be any of the

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regimens used for Class III and IV lupus nephritis. B-cell targeted therapies such as rituximab are gaining favor in idiopathic membranous glomerulonephritis [69] but what this means for pure membranous (Class V) lupus nephritis remains to be seen.

Summary of Therapies for Class III, IV, and V Disease

The Summary of Findings table (Table 25.4) presents various comparisons of treatment and the treatment effects from the most recent Cochrane Kidney and Transplant meta-analysis [17]. A problem with the lupus nephritis RCT literature is that a wide range of treatments has been studied in RCTs that have mostly been too small to assess important clinical outcomes. Most of the trials cited in this chapter are the largest and least susceptible to bias. To explore comparisons and rank therapies that have not been made directly in RCTs, a network meta-analysis was performed [18]. This allowed both direct and indirect comparisons of treatments. Using intravenous cyclophosphamide as the reference treatment, the odds ratio for complete remission was 1.44 (95% CI 1.00–2.06) with mycophenolate mofetil, and 2.69 (95% CI 1.74–4.16) for mycophenolate mofetil combined with tacrolimus. The limitations of this finding have been discussed previously. These treatments were no different with respect to all-cause mortality or ESKD. Overall, this network meta-analysis confirmed that mycophenolate mofetil is similar to intravenous cyclophosphamide, with a better adverse effect profile for both induction and maintenance therapy.

Special Situations

Very Severe or Nonresponsive Lupus Nephritis

Patients with very severe lupus nephritis are often excluded from RCTs or are a subset of participants. There is no universally accepted definition of "severe" and many people would consider any Class III or IV lupus nephritis to be a "severe" kidney-threatening manifestation of SLE. One arbitrary classification of severe that has been advanced defines "severe" as (i) Class IV lupus nephritis with more than 15% crescents and/or glomerular capillary necrosis, (ii) persistence or relapse despite cyclophosphamide, or (iii) Class III or IV lupus nephritis with elevated serum creatinine [75]. This definition has not been used in RCTs but the common theme is that patients with these features usually have elevated serum creatinine.

Patients with very severe lupus nephritis can be treated with the same regimens described above for Class III or IV disease. There is again no accepted definition of "refractory" or "resistant" disease or what constitutes a failure to respond and over what time frame. Both the KDIGO [39] and EULAR/ERA-EDTA [40] Guidelines recommend switching from one regimen to the other (i.e. to mycophenolate if cyclophosphamide used first or to cyclophosphamide if mycophenolate used first). One must also be confident that the optimal dose has been given. These guidelines don't prefer one regimen over the other. A systematic review specifically addressing severe lupus nephritis reported that mycophenolate and cyclophosphamide were equivalent for short-term outcomes but that there was a suggestion from the data that cyclophosphamide had better long-term outcomes such as preservation of kidney function [75]. However, this was not a pooled analysis of individual patient-level data to enable stratification based on kidney function. The ALMS trial reported outcomes in 32 (out of 370) participants who had an eGFR less than 30 ml/min/1.73 m^2 at baseline [76]. Four of 20 patients randomized to mycophenolate mofetil responded, compared to two of 12 patients randomized to cyclophosphamide ($P = 0.9$) but ultimately this study was underpowered to reach any conclusion regarding patients with eGFR less than 30 ml/min/1.73 m^2.

Other therapies with lower levels of evidence that might be "added on" in very unwell patients not responding to mycophenolate or cyclophosphamide include rituximab (discussed above), intravenous immunoglobulin, or a calcineurin inhibitor. Intravenous immunoglobulin has been reported to be beneficial in case reports [77] but the only RCT in lupus nephritis was small ($n = 14$) and compared intravenous immunoglobulin (IVIg) to cyclophosphamide after 6 months of the NIH regimen of intravenous cyclophosphamide [78]. This was really a trial of maintenance therapy and so is difficult to extrapolate as "add-on" therapy in patients with severe disease. Addition of a calcineurin inhibitor such as tacrolimus as in the RCT of "multitarget" therapy with prednisolone, tacrolimus, and mycophenolate mofetil [64] might be considered. However, in addition to the limitations of this trial that have been discussed, kidney function at baseline was relatively well preserved in this trial (80% had eGFR >60 ml/min). Plasma exchange is also suggested as an option in the EULAR ERA-EDTA guideline [40], although an RCT carried out between 1981 and 1986 was stopped early because there was no benefit of plasma exchange added to prednisolone and oral cyclophosphamide [79]. Patients had quite "severe" disease with segmental and proliferative lesions being required for inclusion and a mean serum creatinine at baseline of ~180 umol/l. It remains to be seen whether rituximab or other biologicals will find their place in very severe lupus nephritis.

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Pregnancy and Lupus Nephritis

Most patients with lupus nephritis are women of childbearing age and pregnancy should therefore be discussed early in their course to determine the management to be implemented before conception. Management of pregnancies in women with lupus nephritis requires a multidisciplinary approach and has been recently reviewed [80, 81]. Most women with a history of lupus nephritis have good pregnancy outcomes provided the disease is in remission, and they are lupus anticoagulant negative, not hypertensive, and not non-Caucasian or Hispanic.

Before pregnancy, women with lupus nephritis should be in remission for at least 6 months. Ideally, women will have ceased potentially teratogenic medications such as renin angiotensin system inhibitors, cyclophosphamide, and mycophenolate, and switched to appropriate alternatives. Discontinuation or switching of immunosuppressive medications runs the risk of a flare so should be done before conception and with close monitoring. Hydroxychloroquine is safe in pregnancy and should be continued before, during, and after pregnancy.

Once pregnant, aspirin should be started before 12 weeks gestation and consideration given to anticoagulation in women at risk, such as those with positive lupus anticoagulant or a history of venous thromboembolism.

Close monitoring during pregnancy to detect flares of lupus nephritis or later in pregnancy to detect preeclampsia (and indeed to differentiate one from the other) is essential on top of monitoring for obstetric complications. Management of flares is complicated and depends upon the severity and gestation. Corticosteroids, azathioprine, and calcineurin inhibitors can be used safely at any gestation. Severe or resistant flares bring about very difficult decisions: one must weigh up the risks to the mother and fetus of continuing the pregnancy and using therapies that are more efficacious for the lupus nephritis but less safe for the fetus, against the risks to mother and fetus of delivery of the immediate delivery of the fetus to enable effective therapies.

Withdrawal of Maintenance Therapy

Maintenance therapy can be challenging in lupus nephritis. Once patients are feeling better following induction of remission, it can be hard to convince them that they need ongoing therapy to prevent relapse, particularly when they are experiencing cosmetic and other side effects of corticosteroids. Duration of and withdrawal of maintenance therapy are the subject of debate [82], with the arguments based on whether it is better to minimize treatment toxicity by giving patients time off immunosuppressive therapy or to prevent flares of lupus nephritis, which add to kidney function loss.

The ALMS maintenance trial lasted for 36 months and over this time there were fewer treatment failures or flares with mycophenolate mofetil [32]. Thus, there is evidence to continue mycophenolate as maintenance therapy for 3 years. Beyond this time, evidence for what to do is lacking. In an Italian cohort ($n = 161$) in whom patients in complete remission (proteinuria <0.5 g/day) for 12 months underwent withdrawal of immunosuppression ($n = 73$), 21 (29%) patients had flares during reduction in therapy and 20 of the remaining 52 patients (38%) experienced a flare after withdrawal of maintenance therapy [83]. Overall, these patients received no therapy for 41% of their total follow-up time. These authors recommended that withdrawal of therapy was possible but only after 5 years of maintenance therapy with 3 years in complete remission, and only if done very slowly.

In a group of Argentinian lupus nephritis patients who received maintenance mycophenolate mofetil for 3 years after induction with an NIH cyclophosphamide regimen for 6 months, and who were in complete remission for 12 months (proteinuria<0.5 g/day), a kidney biopsy was performed before mycophenolate mofetil was weaned and ceased over a 6-month period regardless of the kidney biopsy findings [84]. Of the 36 patients who completed the study, 20 were in histological remission at the time of this biopsy (NIH activity index = 0), nine had an activity index 1–2, and seven had an activity index of 3–5. Over the next 24 months 11 patients had a flare of lupus nephritis after ceasing maintenance mycophenolate and 10 of these had an activity index above zero (mainly due to finding endocapillary proliferation and subendothelial deposits). Six of 25 patients who did not flare over 24 months had an activity index of 1 or 2. Although kidney biopsy appears helpful, it must be noted that this study did not demonstrate whether continuation of maintenance immunosuppression if the kidney biopsy was unfavorable would prevent renal flares.

Thus, maintenance therapy should be prolonged and withdrawal of immunosuppression is possible but the benefits (less immunosuppression) and risks (30–40% risk of renal flare) must be carefully weighed up. A kidney biopsy may help to guide the decision.

Renal Replacement Therapy

A major goal of therapy in lupus nephritis is avoidance of ESKD. In the earliest days this meant death for most patients, but now renal replacement therapy is widely available in most, but not all, countries [85]. Although ESKD is an important outcome in the management of lupus nephritis, lupus nephritis is the cause of ESKD in less than 2% of prevalent patients with ESKD [86, 87]. The incidence rate of ESKD is three to four times higher in

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African American patients, who also have a higher mortality [88]. Compared to other patients with ESKD, the patients with lupus nephritis are much younger, more likely to be female, and have less comorbidity from diabetes and cardiovascular disease [87]. Although in the United States mortality rates of patients with ESKD with SLE were similar to people with ESKD who did not have SLE [88], in Australia and New Zealand this was not the case [87]. The adjusted hazard ratio for patient death was 1.33 (1.12–1.58) for patients on dialysis due to lupus nephritis, and 1.87 (1.18–2.98) for kidney transplant recipients, compared to ESKD controls who did not have lupus nephritis.

Despite the possibility of higher mortality, kidney transplant outcomes are still favorable in patients who develop ESKD from lupus nephritis. Five-year renal allograft and death-censored renal allograft survival were 88 and 93%, respectively [87]. Lupus nephritis recurred in 2.3% of kidney transplant in patients in Australia and New Zealand [87], and in 2.44% of kidney transplant recipients in the United States [89]. In the US patients, African American, female and younger patients were more likely to experience recurrence of lupus nephritis, and allograft median survival after recurrence was between 4 and 5 years [89]. The survival of kidneys with recurrent lupus nephritis was similar to those that had rejection and the latter was a far more important cause of graft loss in this study (156 patients lost their graft from recurrent lupus nephritis compared to 1517 from rejection).

Another issue in patients with SLE who develop ESKD from lupus nephritis is whether the SLE becomes "quiescent" or not. Early studies indicate that this is true. In a Dutch population, the mean non-renal SLEDAI was 8.22 ± 6.3 before starting dialysis and 4.41 ± 5.94 when receiving dialysis ($P < 0.01$) and the distribution of the 55 patients with no (SLEDAI = 0), low (SLEDAI = 1–10), or high (SLEDAI > 10) non-renal disease activity was 2, 36, and 17 before dialysis and 19, 28, and 8, respectively, after dialysis [90]. The same authors reported that in 28 patients who received a kidney transplant for lupus nephritis, the number with a non-renal SLEDAI > 10 was 17 before dialysis, three during dialysis and none after transplant [91]. In contrast, a Brazilian study compared 57 patients on dialysis with SLE to 57 controls and defined lupus activity by the SLEDAI score or if patients required prednisolone 20 mg daily or greater [92]. The proportion with SLEDAI scores of 0, 1–3, 4–7, and ≥8 were 19%, 44%, 19%, and 18% for the SLE patients and 63%, 33%, 4%, and 0% for the non-SLE patients, respectively. Thus, SLE disease activity should be actively considered even after renal replacement therapy becomes the primary focus of management.

Conclusion

Lupus nephritis is a kidney-threatening manifestation of SLE for which a number of treatments have been studied in RCTs over many years. However, there is still a long way to go to increase the complete remission rates with these regimens or newer therapies while at the same time reducing the toxicity of treatment. Acquiring good evidence remains a challenge due to the heterogeneity of the disease itself and difficulties with recruiting large numbers of patients into treatment trials, the need to consider both induction and maintenance therapy, and the long follow-up required to measure outcomes such as renal relapse after remission, loss of kidney function, and ESKD.

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26

Hemolytic Uremic Syndrome

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Introduction

The Nomenclature of TMA

Thrombotic microangiopathy (TMA) describes a group of highly diverse disorders in children and adults that is defined by microvascular thrombosis with characteristic abnormalities of the vascular endothelial lining. Clinically, TMA is characterized by a triad including microangiopathic hemolytic anemia (MAHA), thrombocytopenia, and organ dysfunction, primarily of the kidneys [1–3].

TMA can be hereditary (either familial or sporadic) or acquired, and it can also be primary or secondary to numerous different conditions including infections, immunological diseases, glomerular diseases, stem cell and solid organ transplantation, drugs, cancer, malignant hypertension, and pregnancy [2–4]. Thus, the classification of TMA is challenging and debatable, and today there is no uniform accepted nomenclature in the literature or in clinical practice. Historical classifications were based on clinical features, mainly distinguishing between thrombotic thrombocytopenic purpura (TTP), which is clinically characterized by predominant neurologic involvement and is more common in adults, and hemolytic uremic syndrome (HUS), which involves primarily the kidneys and is more common in children. HUS has been further divided into two diseases, Shiga toxin-producing *Escherichia coli* (*E. coli*)-related HUS (STEC-HUS, *typical* HUS) and *atypical* hemolytic uremic syndrome (aHUS), which has been used for any TMA type that is not related to STEC-HUS or TTP [2–6]. More recent classifications which are based on pathophysiology have evolved due to greater understating of the underlying mechanism of the different types of TMA [2, 3, 5]. We, among other authors, opt to further classify the highly heterogeneous group aHUS according to the different etiologies which cause this syndrome, as shown in Figure 26.1. As aHUS is known to be caused by complement dysregulation the term complement-mediated TMA is preferred. Rare primary TMA are not related to complement may be termed primary noncomplement TMA. All other forms of TMA that are have been included in the aHUS group are classified as secondary TMA, which should be termed based on the underlying disorder, i.e. infection-related TMA, autoimmune disorder-related TMA, drug-related TMA, etc.

The pathophysiology-based classification used in this chapter provides a practical guide for clinicians facing a patient with an undiagnosed TMA. However, the classification of TMA is still evolving, and it is likely that with time new classifications will be suggested as despite great advancement in the revelation of molecular basis of TMA over the last 20 years, a considerable number of cases (up to 30%) are still classified as "unknown" or "idiopathic" TMA, and further pathophysiological insights can be expected [2–4, 7, 8] Table 26.1.

The TMA Spectrum

The first report of TMA, presumably TTP, dates from 1924, when Moschcowitz described a 16-year-old girl with pallor, purpura, and hemiparesis who died with cardiac failure. On autopsy, thrombi were seen in terminal arterioles and capillaries in many organs [1, 3]. It was not until 1982, however, that unusually large multimers of von Willebrand factor (vWF) were found to accumulate in the plasma of patients with chronic TTP, leading to occlusive microvascular platelet thrombi. Subsequently, a deficiency (enzyme activity <10%) of a disintegrin and metalloproteinase with a thrombospondin type 1 motif member 13 (ADAMTS13), a vWF cleaving-protease, was found to be the cause of the

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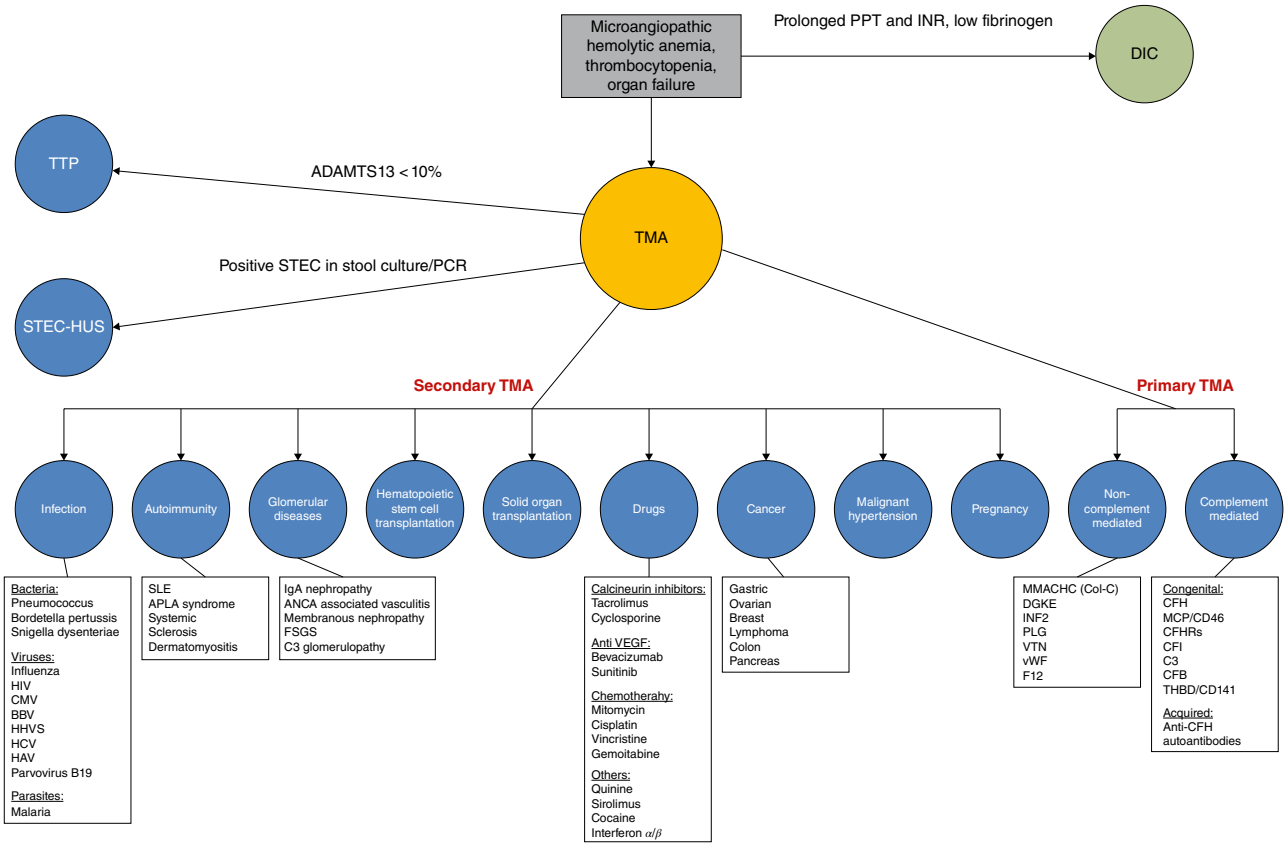

Figure 26.1 Classification and diagnostic workup of TMA. ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif member 13; ANCA, antineutrophil cytoplasmic antibody; APLA, antiphospholipid antibody; CFB, complement factor B; CFH, complement factor H; CFHR, complement factor H related protein; CFI, complement factor I; CMV, cytomegalovirus; DGKE, diacylglycerol kinase ε; DIC, disseminated intravascular coagulation; EBV, Epstein–Barr virus; F12, factor XII; FSGS, focal segmental glomerulosclerosis; HAV, hepatitis A virus; HCV, hepatitis C virus; HHV6, human herpes virus 6; HIV, human immunodeficiency virus; HUS, hemolytic uremic syndrome; IgA, immunoglobulin A; INF2, inverted formin-2; INR, international normalized ratio; MCP/CD46, membrane cofactor protein; MMACHC,– methylmalonic aciduria and homocystinuria type C protein; PCR, polymerase chain reaction; PLG, plasminogen; PTT, partial thromboplastin time; SLE, systemic lupus erythematosus; STEC, Shiga toxin producing *E. coli*; THBD/CD141, thrombomodulin; TMA, thrombotic microangiopathy; TTP, thrombotic thrombocytopenic purpura; VEGF, vascular endothelial growth factor; VTN, vitronectin.

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Table 26.1 Summary of diagnostic tests in TMA.

Test	What does it measure?	Comments
TMA diagnosis		
Creatinine, urea	• Kidney function tests	• Both are elevated in TMA and signify AKI
Hemoglobin, haptoglobin, LDH, direct antiglobulin (coombs) test, blood film	• MAHA markers	• Low hemoglobin and haptoglobin • High LDH • Negative coombs test (except in pneumococcal TMA) • Fragmented red blood cells (schistocytes) on blood film
Platelets	• Platelet count	• Thrombocytopenia is usually the first sign to appear and increase in platelets count is usually the first sign of recovery
Further assessment of kidney involvement		
Urine analysis, urine protein, or albumin to creatinine ratio	• Degree of hematuria and proteinuria	• Proteinuria is often nephrotic-ranged • Hematuria is often the first sign of relapse of complement-mediated TMA
Kidney US + Doppler	• Structure of the kidneys, patency of kidney vessels	• Findings in TMA are not specific, however kidney US + Doppler may aid in excluding other clinically relevant kidney diseases such as renal vein thrombosis
Assessment of extra-renal involvement		
Brain MRI	• Structure of the brain	• For assessment of neurologic complications; findings include posterior reversible encephalopathy syndrome (PRES), hemorrhage, infarcts, edema, and others
Chest x-ray	• Structure of the lungs and heart	• For assessment of pulmonary complications; findings include pulmonary edema, pulmonary hemorrhage, and others
ECG, echocardiography	• Heart structure and function, arrhythmias	• For assessment of cardiac complications; findings include left ventricular hypertrophy, cardiomyopathy, valvular disease, myocardial infarction, and others
Abdominal US/CT	• Structure of abdominal viscera	• For assessment of gastrointestinal complications; findings include cholelithiasis, pancreatitis, hepatitis, and others
AST, ALT, GGT	• Liver enzymes tests	• For assessment of hepatitis as a complication of TMA or as a cause of TMA (i.e. in HAV or HCV)
Amylase, lipase	• Pancreatic enzymes tests	• For assessment pancreatitis as a complication of TMA
Exclusion of DIC		
PTT, INR, fibrinogen	• Basic coagulation tests	PTT and INR are prolonged and fibrinogen is low in DIC, while in TMA these tests are usually normal
Diagnosis/exclusion of TTP		
ADAMTS13 activity	• Activity of the vWF cleaving-protease	• Activity level >10% rules out TTP
Diagnosis/exclusion of STEC-HUS		
Stool culture and/or PCR	• Microbiologic tests for STEC identification	• In STEC-HUS these tests are positive for *E. coli* O157:H7 or other less common STEC
Diagnosis/exclusion of secondary TMA		
Blood/stool cultures, viral serology/PCR	• Microbiologic tests for non-STEC pathogens which may cause TMA (i.e. blood culture for pneumococcus, stool culture for *Shigella dysenteriae*, serology for HIV, PCR for influenza)	• For diagnosis/exclusion of infection-related TMA in the relevant clinical context

(*Continued*)

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Table 26.1 (Continued)

Test	What does it measure?	Comments
ANA, anti dsDNA (SLE) Lupus anticoagulant, anticardiolipin antibodies (APLA) Antitopoisomerase I, anti-RNA polymerase III, anticentromere antibody (systemic sclerosis)	• Autoimmune antibodies in SLE • Autoimmune antibodies in APLA • Autoimmune antibodies in systemic sclerosis	• For diagnosis/exclusion of autoimmune disease-related TMA in the relevant clinical context
ANCA, C3, IgA	• Markers of different types of GN	• For diagnosis/exclusion of GN-related TMA in the relevant clinical context • Positive ANCA may signify ANCA-associated glomerulonephritis (GN) • Low C3 is not specific and can be seen in many GN as well as in complement-mediated TMA • Elevated IgA in the right clinical context may suggest IgA nephropathy, but normal IgA is common in this entity
Kidney biopsy	• Histopathology of the kidney	• For diagnosis/exclusion of GN-related TMA and of solid organ transplantation-related TMA in the relevant clinical context • Kidney biopsy is often needed for the diagnosis of the specific type of GN, and of TMA associated with solid organ transplantation, but it is not required for the diagnosis of TMA
Urine/serum β-HCG	• Pregnancy test	• For diagnosis/exclusion of pregnancy-related TMA • Should be part of the diagnostic work-up of any case of TMA in a woman of childbearing age
Blood homocysteine, blood methionine, urine methylmalonic acid	• Molecules related to cobalamin metabolism	• For diagnosis/exclusion of cobalamin C-related TMA • Blood homocysteine and urine methylmalonic acid are elevated in cobalamin C-related TMA, while blood methionine is reduced
Diagnosis/exclusion of primary noncomplement-mediated TMA		
Genetic tests of DGKE, MMACHC, INF2, PLG, VTN, vWF, F12	• Screening for pathogenic variants in non-complement related genes	• For diagnosis/exclusion of primary, noncomplement-mediated TMA • DGKE gene should be tested in infantile onset TMA • MMACHC gene should be tested to confirm the diagnosis of cobalamin C-related TMA if the screening biochemical tests (blood homocysteine and methionine, urine methylmalonic acid) suggest this disorder
Diagnosis of primary, complement-mediated TMA		
Genetic tests of CFH, MCP/CD46, CFHRs, CFI, C3, CFB, THBD/CD141	• Screening for pathogenic variants in complement-related genes	• For molecular confirmation of the clinical diagnosis of the congenital form of complement-mediated TMA
Anti CFH-autoantibodies	• Screening for anti-CFH autoantibodies	• For diagnosis/exclusion of the acquired form of complement-mediated TMA
Further investigation in primary complement-mediated TMA		
CH50, AP50, CFH activity	• Complement functional assays	• Low CH50 may result from consumption of complement factors in complement-mediated TMA but also from other causes such as hepatic disease. It may also be marker of eculizumab therapy • Low AP50 is common during the active phase of complement-mediated TMA but may be low also in STEC-HUS and other disorders • Decreased CFH activity implies a CFH mutation or anti-CFH autoantibodies

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Table 26.1 (Continued)

Test	What does it measure?	Comments
C3, C4, CFH, CFI, CFB, MCP/CD46	• Levels of complement components and inhibitors	• C3 is low in only 30–50% of patients with complement-mediated TMA (nonspecific) • Low C4 is associated with complement classical pathway disorders and not with complement-mediated TMA • Low CFH, CFI, or MCP/CD46 may signify mutations in these genes
C5b-C9, C3d, Bb	• Degree of complement activation	• High C5b-9 levels (membrane attack complex) expected in active complement mediated TMA; may be also seen in STEC-HUS • High C3d in combination with low C3 levels associated with C3 consumption rather than deficiency • High Bb and low CFB level found in both, complement mediated TMA and STEC-HUS

disease. In hereditary TTP, recessive mutations in the gene encoding for ADAMTS13 are responsible for the deficiency, while autoantibodies against ADAMTS13 cause the more common acquired TTP [1–3, 9, 10]. TTP was historically almost universally fatal, but the systematic use of plasma exchange (PE) therapy decreased mortality to <10% [2].

With a frequency of 1–3/100 000, STEC-HUS is the most common type of TMA in children [2, 7, 11]. The term "hemolytic uremic syndrome" was first proposed in 1955 for children with renal failure, anemia, and thrombocytopenia, and subsequently a preceding hemorrhagic colitis was described [12, 13]. In 1982, during an investigation of outbreaks of hemorrhagic colitis, *E. coli* O157:H7 was identified as a pathogen and in the same year the association between HUS and STEC was described [1, 3, 11]. The terms "D+ HUS" (diarrhea positive HUS) for HUS caused by STEC or other rarer enteric bacteria and "D−HUS" (diarrhea negative HUS) for other TMA should be deferred, as some (albeit rare) patients with STEC-HUS do not have diarrhea, while up to 30% of patients with complement-mediated TMA may have diarrhea at presentation [2, 5].

Complement-mediated TMA is primarily caused by mutations in complement factors (regulators and/or activators), leading to uncontrolled activity of the complement alternative pathway (AP), but it can be also caused by acquired abnormalities such as antibodies against complement factor H (CFH) [2, 4, 5, 14].

Primary noncomplement-mediated TMA is caused by mutations in genes that are typically not related to the complement system. The first of these is cobalamin C-related TMA, which is a hereditary metabolic cause of TMA caused by recessive mutations in methylmalonic aciduria and the homocystinuria type C protein (MMACHC) gene. Patients usually present in infancy with diverse developmental abnormalities and primarily neurologic symptoms. However, TMA can also occur in these patients as abnormalities in cobalamin (vitamin B12) metabolism may lead to endothelial dysfunction. This disorder is uncommon but relevant, since both diagnostic tests (serum homocysteine and urine methyl-malonic acid levels) and efficient therapies (with hydroxycobalamin, folinic acid, and betaine) are available, simple, and inexpensive [3, 15, 16] Table 26.1. Another disorder in this group is diacylglycerol kinase ε (DGKE)-related TMA. Homozygous mutations in DGKE result in infantile aHUS, but may also cause membranoproliferative glomerulonephritis (MPGN) or a clinical and pathological overlap between these two disorders. The mechanism is unknown, but may be related to protein kinase C-mediated upregulation of prothrombotic factors. Proteinuria, often nephrotic, is a major component of this disorder and most patients slowly progress to end-stage renal disease (ESRD) [2–4, 6, 17–19]. Recently, patients from two different families were found to have TMA presumably caused by mutations in inverted formin-2 (INF2) gene, which is also known to be involved in focal and segmental glomerulosclerosis (FSGS). Interestingly, two patients from one family were also diagnosed with the hereditary peripheral neuropathy disorder Charcot–Marie–Tooth [20]. It is likely that TMA-causing mutations in novel genes will be added to this group of primary noncomplement TMA in the future.

Many diseases and conditions may lead to secondary TMA. Infectious agents include bacteria other than STEC, which can produce Shiga toxin (such as *Shigella dysenteriae*), *Streptococcus pneumoniae*, and viruses such as HIV and influenza A and B [2, 7, 21–24]. TMA may complicate autoimmune diseases such as systemic lupus erythematosus (SLE), catastrophic antiphospholipid syndrome (CAPLS), and systemic sclerosis [2, 25–28]. It can be seen in association with other glomerular disorders, including immunoglobulin

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A (IgA) nephropathy, anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis, and others, although this may be a histopathologic finding only without the typical clinical findings [2, 29, 30]. TMA is a known and multifactorial complication of hematopoietic stem cell transplantation [31–34]. It can also complicate solid organ transplantations, including kidney transplants, either as recurrence of known complement-mediated TMA post-transplant or, more commonly, de novo [7, 35, 36]. Many different drugs have been suspected as a cause of TMA, though a clear evidence for causal association has been shown with relatively few. Quinine is an example of a drug which may cause TMA by immune mechanism, while calcineurin inhibitors (CNI) may represent drugs which cause TMA via direct toxicity [2, 3, 37, 38]. Cancer has long been associated with risk of TMA, either caused by malignancy itself or more often resulting from anticancer therapy [2, 39, 40]. Malignant hypertension with concomitant TMA places a clinical dilemma as any TMA can cause hypertension which may be severe, therefore it may not be clear which entity is the cause and which is the consequence [2, 41–44]. Finally, pregnancy and the postpartum period are associated with various TMA syndromes: complement-mediated TMA, TTP, and the TMA-like syndrome HELLP (hemolysis, elevated liver enzymes, and low platelets), which is related to eclampsia [45–48]. Importantly, in nearly all of these secondary forms of TMA abnormalities in complement-related genes have been described in some patients, many of whom were treated successfully with eculizumab, the complement C5-inhibitor [25, 26, 39, 41, 45, 49, 50]. This implies that a proportion of patients with secondary forms of TMA actually have primary complement-mediated TMA and the secondary condition (i.e. pregnancy, drug, infection, etc.) constitutes a trigger or a "second hit" which is required for developing the full picture of TMA, rather than the primary cause of it [2, 4, 21, 25, 26, 34, 41, 42, 45, 46, 48, 49].

The following will focus on the epidemiology, pathophysiology, clinical manifestations, diagnosis, prognosis, and treatment of two entities of the TMA spectrum: STEC-HUS and complement-mediated TMA.

Epidemiology

In children, 85–90% of TMA cases are caused by infection with STEC. STEC-HUS is more frequent in children than in adults, with median age around 2 years, although adults have more severe disease with higher mortality [3, 4]. The annual incidence in Europe and North America is 1.9–2.9 cases per 100 000 children <3–5 years, and it decreases with age [4]. The predominant cause in most of the world is *E. coli* O157:H7 and most occurrences are sporadic [3, 7, 11]. However, outbreaks of O157:H7 or other serotypes are also common, and the most significant recent outbreaks occurred in Germany in 2011 (*E. coli* O104/H4), in Oklahoma, USA, in 2008 (*E. coli* O111/NM), and in Ontario, Canada, in 2000 (*E. coli* O157:H7) [51–54]. Most *E. coli* O157:H7 infections and HUS occur in summer and autumn [5, 9]. The primary reservoir of *E. coli* O157:H7 is the intestinal tract of cattle, and it is more common in rural areas and in countries with high-density cattle raising, such as Scotland and Argentina. Ground beef, lettuce, sprouts, municipal water, and many other sources have been all recognized as major transmission vehicles of STEC, while airborne and person-to-person transmission have also been described [11, 55, 56]. The risk of developing HUS after STEC-colitis is around 10% in sporadic infections, and up to 20% in epidemic outbreaks [4, 7, 11, 55].

Complement-mediated TMA accounts for 5–10% of all HUS cases, with incidence of 0.5–2 cases per million per year [5, 7, 8, 57]. It can occur in children and adults, and may be sporadic (most often) or familial. Genetic mutations affecting genes related to the complement alternative pathway or autoantibodies against CFH are found in 50–60% of cases of complement-mediated TMA [4–6, 8, 57–59]. In 40–50% of patients clinically diagnosed with complement-mediated TMA, no specific cause, genetic or autoimmune, is identified. CFH mutations were the first to be described and are the most common abnormality responsible for complement-mediated TMA, accounting for 24–27% of cases [6, 58, 60, 61]. The second most common mutations (7–9%) are found in the gene encoding for membrane cofactor protein (MCP or CD46), followed by complement factor I (CFI) and complement component 3 (C3) mutations, each of which accounts for 4–8% of cases [6, 58, 60–63]. Mutations in complement factor B (CFB), thrombomodulin (THBD or CD141), and complement factor H-related proteins (CFHRs) are responsible together for 5–10% of cases [6, 58, 60, 61, 64]. Anti-CFH autoantibodies account for 10–15% of cases and are frequently associated in deletions of CFHR1 and 3 [6, 57, 58, 60, 61]. Five to ten percent of complement-mediated TMA patients carry more than one mutation [57, 58, 65]. The presence of one or more mutation and/or the presence of specific genetic risk variants, as discussed in the next section, may increase the risk of disease manifestation [3, 4, 6, 7, 56–58, 60, 65].

Pathophysiology

The common pathologic basis of all TMA is injury to the vascular endothelium with subsequent microvascular thrombosis, which leads to consumptive thrombocytopenia, MAHA, and kidney and other organs injury [2–4, 56, 66].

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STEC-HUS

There has been great advancement in understanding the mechanism of the disease since the first description of STEC-HUS. However, one of the main questions regarding STEC-HUS pathophysiology – why only 10–20% of patients with STEC infection develop HUS –remains unanswered [2–4].

Enteric STEC infections are almost never accompanied by bacteremia. Rather, the systemic complications, such as HUS, and at least partially also the intestinal manifestations, are caused by the (Shiga) toxin, which is the key factor in the pathogenesis of STEC-HUS [7, 11]. There are two kinds of toxin, Shiga toxins 1 and 2 (Stx1 and Stx2), with the latter being more virulent. Both toxins are made of two subunits: subunit A is an N-glycosidase which inhibits protein synthesis and subunit B binds to globotriaosylceramide (Gb3, also known as CD77) on the surface endothelial, mesangial, and epithelial (podocytes and tubular) cells, as well as blood cells including monocytes, polymorphonuclear cells, and platelets [3, 4, 7, 11, 55, 56]. The strong expression of Gb3 on glomerular endothelial cells, as well as the apparent propensity of the glomerular circulation to endothelial damage and occlusion, is thought to be the explanation of why the kidney is the main organ involved in STEC-HUS [2, 7, 11, 56]. After inducing hemorrhagic colitis, Stx binds to these blood cells and circulates in the bloodstream. Stx is released from blood cells within microvesicles, a process which both facilitates its transport to the target cells in the kidney and enables the toxin to evade the host immune system. These microvesicles were also shown to be prothrombotic and thus may contribute to the pathogenesis of HUS in several mechanisms [67, 68]. The toxin is subsequently internalized to endothelial and epithelial kidney cells by endocytosis, splits into its A and B subunits, and then – via its B subunit – inhibits the 28S unit of ribosomal ribonucleic acid (rRNA) and thus protein synthesis. This step induces a stress response that can lead to apoptotic cell death [2, 3, 11, 55, 56]. Another effect of Stx is induction of thrombosis by enhancement of tissue factor expression, increasing thrombin formation and vWF secretion, inhibition of fibrinolysis, and direct platelets activation [3, 55, 56, 66, 69]. In addition to its apoptotic and prothrombotic effects, Stx induces inflammation by upregulation of cytokines, chemokines, and adhesion molecules [2, 3, 7, 70].

Complement activation, which is responsible for complement-mediated TMA, has been noted to be involved in STEC-HUS as well over the last 10 years [71–77]. There is evidence of Stx-induced complement activation via both the mannose-binding lectin (MBL) and the alternative complement pathways [71, 72, 74, 77]. Moreover, Stx can bind CFH and significantly delay its activity as a cofactor for CFI-mediated cleavage of C3b on the surface of the endothelial cell, thereby markedly reducing the regulatory activity of CFH on complement activation [74, 76].

Complement-mediated TMA

Dysregulation of the complement alternative pathway is the cause of complement-mediated TMA [2–4, 6–8, 78]. The complement system is part of the innate immune system, which has an important role in targeting and killing of pathogens, and induction of an inflammatory response. It consists of >30 plasma and membrane-bound proteins and has three activation pathways: classical, MBL, and alternative. Activation of each of these pathways leads to production of protease complexes termed C3 and C5 convertases that cleave C3 and C5, respectively, eventually resulting in the formation of the membrane-attack complex (MAC; C5b-9), which causes cell lysis. In addition, activation of C3 and C5 results in the generation of the highly reactive anaphylatoxins C3a and C5a, respectively [2, 3, 6, 8, 78, 79].

Unlike the other two pathways, the alternative pathway is constitutively active as a result of spontaneous, hydrolysis-mediated generation of C3b on both pathogen and normal host cells, therefore requiring tight regulation to limit activation both spatially and temporally [2, 3, 6, 79, 80]. The plasma regulators are CFH and CFI, while MCP (CD46), decay accelerating factor (DAF/CD55), protectin (CD59), and complement receptor 1 (CR1/CD35) are membrane-bound regulators [4, 7, 78, 79]. Thrombomodulin (CD141), encoded by THBD gene, is another membrane-bound protein which is an antithrombotic factor, but also has complement inhibitory activity [6, 8, 81, 82]. Loss of function mutations in these regulatory genes or gain of function mutations in effector genes such as CFB and C3 leads to complement dysregulation and overactivation, eventually causing injury of the vascular endothelium and TMA [3, 4, 6, 7, 60, 62, 64, 78, 79, 83–88].

Pathogenic mutations identified in patients with complement-mediated TMA include nonsense and missense mutations, deletions, splice site changes, and complex rearrangements. Most of these changes are heterozygous, even though many family members with heterozygous mutations are asymptomatic. Thus, the penetrance of these mutations is incomplete and is known to increase with age and with the presence of additional risk factors [2–4, 6, 7, 57, 61]. Genetic risk factors include a second mutation or genetic variants such as specific single nucleotide polymorphisms in CFH or MCP genes, copy-number variations in CFHR 1 and 3, and fusions genes of the CFHRs region [3, 4, 6, 7, 57, 59, 64, 65, 89]. Additionally, there are known environmental triggers for complement-mediated TMA episodes or relapses, including infections, drugs, and pregnancy [2, 6, 7, 45, 46, 48, 79, 90].

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Acquired complement-mediated TMA occurs in the form of autoantibodies against CFH [2, 6, 8, 91–94]. CFH autoantibodies identified in complement-mediated TMA patients exclusively bind to epitopes located to the C-terminus of CFH, thus preventing binding of CFH to endothelial surfaces and C3 [6, 8, 93, 95]. There is a strong (but so far unexplained) association between the homozygous deletion of complement factor H-related proteins 1 and 3 (CFHR1 and CFHR3) and the presence of anti-CFH autoantibodies [2, 6, 8, 92–94, 96].

Clinical Manifestation

The clinical symptoms of TMA reflect anemia, thrombocytopenia, and renal or other organ involvement, and include pallor, fatigue, shortness of breath, oliguria, and edema [4]. In almost all cases of STEC-HUS, manifestations are preceded by severe abdominal pain and diarrhea, which start 2–12 days (average 3) after ingestion of contaminated vehicle. The diarrhea becomes bloody in up to 90% of patients, and 30–60% of patients have fever and vomiting. TMA manifestations in those patients who develop the syndrome occurs after the colitis improves, approximately a week after the onset of diarrhea [3, 4, 7, 11]. Half of complement-mediated TMA episodes are triggered by intercurrent events, including upper respiratory tract infection, gastroenteritis, vaccination, and childbirth [4, 57, 58]. Renal involvement includes hematuria, proteinuria (commonly nephrotic ranged), oliguria, and hypertension, which may be severe, especially in complement-mediated TMA. The severity of renal involvement is greater in adults, and in general varies between mild nephritis without acute kidney injury (AKI) to severe anuric AKI, and many patients with both STEC-HUS and complement-mediated TMA require acute dialysis [3, 4, 7, 97].

Extrarenal manifestations occur in 19–38% of patients with STEC-HUS and complement-mediated TMA [2, 4–6, 61, 98]. Possible mechanisms include vascular injury caused by Stx in STEC-HUS and by complement activation in complement-mediated TMA, as well as hypertension and uremia caused by renal failure [4, 5, 7, 11, 98, 99]. Neurologic involvement is the most common extrarenal manifestation in both STEC-HUS and complement-mediated TMA and includes seizures, alteration in consciousness, hemiparesis, vision loss, and other rarer symptoms [4, 5, 11, 58, 97–100]. Gastrointestinal involvement is also common and includes diarrhea, vomiting, gastrointestinal bleeding, cholelithiasis, pancreatitis, and hepatitis [2, 4, 61, 98, 99]. Cardiac complications include left ventricular hypertrophy, dilated or hypertrophic cardiomyopathy, valve insufficiency, myocardial infarction, and intracardiac thrombus [4, 7, 11, 57, 98, 99]. Other extrarenal manifestations include pulmonary edema, hemorrhage and embolism, ocular complications, and gangrenous fingertips [4, 11, 92, 97–99]. In complement-mediated TMA extrarenal manifestations are more common during the initial 6 months post presentation, but can also occur during the chronic phase [61].

Diagnosis

Figure 26.1 presents a general approach to diagnosis of TMA. The defining laboratory features in TMA include elevated creatinine and urea, thrombocytopenia, and signs of MAHA. The latter include low hemoglobin, high lactate dehydrogenase (LDH), low haptoglobin, negative direct antiglobulin (coombs) test (except in pneumococcal TMA), and evidence of fragmented red blood cells (schistocytes) on peripheral blood film. Urinalysis usually shows hematuria and proteinuria [2, 4, 5, 101].

The typical findings on kidney biopsy are thickening of arterioles and capillaries, endothelial swelling and detachment, subendothelial accumulation of proteins and cell debris, and fibrin and platelet-rich thrombi obstructing vessel lumina. However, biopsy is not requisite for the diagnosis of TMA, and it cannot distinguish between the different etiologies of TMA [2, 3, 5, 6, 8].

The first step in the diagnostic process of a patient with the triad of AKI, MAHA, and thrombocytopenia, who presumably has TMA, is to exclude the other entity which can present with these manifestations, disseminated intravascular coagulation (DIC). DIC and TMA can be easily distinguished by sending coagulation tests as in the former partial thromboplastin time (PTT) and prothrombin time (PT) or international normalized ratio (INR) are prolonged and fibrinogen level is low, while in the latter these tests should be normal [2, 102, 103].

The next step is investigation for the cause of TMA, which is crucial because different forms of TMA have completely different treatments. Since TTP is a common cause of TMA, especially in adults, and it can efficiently be treated via plasma exchange (PE), one of the first priority tests should be the detection of the activity level of ADAMTS13. Activity level >10% rules out TTP [2, 4, 5, 104]. The other common cause of TMA, especially in children, is STEC-HUS, and therefore one should always exclude this cause before diagnosing rarer types of TMA. In STEC-HUS, stool cultures should be positive for *E. coli* O157:H7 or other less common STEC, and another commonly used diagnostic method is polymerase chain reaction (PCR) assay for the bacteria or Stx [11, 55, 105].

Exclusion of a secondary TMA (related to infection, autoimmunity, glomerular disease, stem cell and solid organ

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transplantation, drugs, cancer, malignant hypertension, or pregnancy) follows the clinical context, history and physical examination, and additional ancillary tests, depending on the specific clinical presentation. Screening for cobalamin C-related TMA, with serum homocysteine and urine methylmalonic acid levels, which are typically high, is recommended [2, 4, 6].

In only 30–50% of patients with complement-mediated TMA are C3 levels low, and they may also be low in other types of TMA [5, 6, 104]. More specific assays such as CH50 (measuring total complement activity), AP50 (measuring alternative pathway activity), CFH functional assay, and levels of complement activation markers such as C3d and C5b-9 allow for insights into functional aspects of the complement system. Additionally, comprehensive screening of all genes currently known to be involved in complement-mediated TMA is recommended, including CFH, MCP/CD46, CFI, C3, CFB, CFHR 1, and 5, and THBD/CD141 [2–6, 57]. Infants should also be tested for mutations in DGKE, which is responsible for a form of primary noncomplement TMA [2, 4, 17, 18, 57]. Finally, anti-CFH autoantibodies should be tested for to diagnose the known acquired form of complement-mediated TMA [5, 6, 57, 104].

However, complement functional assays are available only in few laboratories and, similarly to genetic testing, require long time to being processed. Moreover, only 50–60% of patients with presumed complement-mediated TMA are eventually found to have a disease causing mutation in one of the above-mentioned genes. Thus, complement functional and genetic tests are important to confirm the diagnosis, inform outcome, and guide treatment, but they do not play a role in the acute diagnosis of complement-mediated TMA, which remains clinical and is established after excluding all other forms of TMA. In the era of an efficacious anticomplement therapy, which may completely change outcome, the diagnosis of complement-mediated TMA should be made in a timely manner. Therefore, every patient with no obvious clinical picture of STEC-HUS, TTP, or a secondary TMA, with ADAMTS13 activity >10% and with STEC negative stool culture or PCR should be diagnosed with complement-mediated TMA, at least until proven otherwise, and treated with anticomplement therapy [2, 4, 6, 101, 103].

Prognosis

STEC-HUS

When first described, the mortality of STEC-HUS was >30% for all cases. In more recent years, with an improved understanding of pathogenesis, recognition, and early dialysis for oligoanuric patients, the acute mortality rate has dropped to 1–4% [106, 107]. CNS involvement is the most common cause of death, occurring in <50% of children with STEC-HUS [108], with cardiac failure, pulmonary hemorrhage, bowel perforation, and electrolyte imbalances following [106].

Early literature identified the following risk factors predicting a more severe course of postdiarrheal HUS: oligoanuria, younger age (<2–3 years), high initial leukocyte count, hypertension, and severe colitis [106, 109–115]. More recent studies have found that CNS involvement, high hemoglobin, and low sodium levels were the best predictors of death in STEC-HUS patients [108].

CNS involvement may include seizures, hemiplegia or hemiparesis, extrapyramidal syndrome, and coma. MRI findings in patients showed that all parts of the CNS were susceptible to injury, and that there was no correlation between localization of injury and final prognosis. The overall prognosis in this patient group was poor with nine patient deaths and 13 with severe sequelae [100]. Of note, the exact mechanism resulting in CNS injury may differ from that of renal involvement and treatment may require a multifaceted approach [116].

As mortality has improved markedly in the past few decades, long-term sequelae may still require management in STEC-HUS patients. Persistent hypertension is seen in 5–15%, progression to CKD in up to 18% of children, and ESRD in approximately 3% of patients. Given the multiorgan involvement, complications of the nervous system, heart, gut, biliary system, and pancreas may need to be followed over time [106].

Complement-mediated TMA

The prognosis of complement-mediated TMA has classically been poor, with most patients developing ESRD within 2 years of presentation [5]. However, in the past decade the management of complement-mediated TMA has undergone a paradigm shift and the associated outcomes have evolved as well.

Complement-mediated TMA carried a mortality rate of up to 70% before the advent of terminal complement blockade [7]. Since the monoclonal C5 antibody eculizumab has widely become available, short-term mortality has fallen and outcomes have improved significantly [117–119]. At this time, many long-term outcomes of eculizumab-treated complement-mediated TMA patients have yet to become available.

As a disorder of complement dysregulation, identifying specific mutations can offer prognostic information in complement-mediated TMA. Mutations in CFH [61], CFI, and C3 have been associated with a worse prognosis, while MCP/CD46 mutation carriers with childhood disease onset have shown improved outcomes. Adult patients with no

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identifiable mutations in a study of 214 patients with complement-mediated TMA were found to have similarly poor prognoses as the above-mentioned subgroups, where children without identifiable mutations had similar outcomes to the MCP/CD46 mutation group [120].

Interestingly, outcomes from this study show discrepancies based on the age of the patient: children with complement-mediated TMA have a higher mortality compared to adults (6–7% vs. <1% at 1 year), whereas progression to ESRD after the first episode was more frequent in adults (46% vs. 16%). Approximately 56% of adult patients progress to ESRD within the first year of illness [120]. Sex, race, time from initial presentation to diagnosis, and family history of complement-mediated TMA do not appear to be associated with risk of progression to ESRD [61].

A substantial number of patients may also develop extrarenal complications in both the chronic and acute phases. Gastrointestinal, cardiovascular, CNS, and pulmonary manifestations may impact adults and children and may require long-term follow-up [61].

The advent of the terminal complement blockader eculizumab has fundamentally shifted the trajectory of illness in complement-mediated TMA, but the disease process still carries considerable morbidity and mortality risk both in the acute and chronic phases.

Treatment

General Supportive Therapy for all TMA

Acute Kidney Injury

Once established, TMA care requires management of oliguric AKI. Fluid and electrolyte intake and output should be carefully calculated and reassessed as patients may be anuric and require fluid restriction. Dietary and other intake restrictions on electrolytes such as potassium or phosphate may be required as the GFR declines. Patients may also have intolerance to oral food intake and may require assistance with enteral feeds or parenteral nutrition. Hypertension management may also be necessary in these patients [121].

Anemia and Thrombocytopenia

Anemia and thrombocytopenia may be profound, and providers are often faced with a dilemma regarding the need for transfusion of blood products. In addition to the typical risks of blood transfusion (e.g. allergic reaction, infection, electrolyte derangement), one must be cognizant of the exposure of the patient to donor antigens and the subsequent production of donor-specific antibodies. In a patient with a potential risk of developing CKD and who may potentially require kidney transplantation, clinicians must be judicious regarding blood transfusions [121, 122].

A patient whose serum hemoglobin concentration is below the center-specific transfusion threshold, but who is well-perfused, hemodynamically stable, and whose other hemolytic markers (LDH, haptoglobin, reticulocyte count) suggest declining hemolysis may be managed expectantly, whereas a patient with a low hemoglobin, ongoing hemolysis, and any signs of cardiovascular instability would likely necessitate a blood transfusion.

Thrombocytopenia can be significant in all TMAs. However, as previously detailed, platelets may contribute to microthrombi formation and may aggravate the underlying microangiopathic cascade, worsening symptoms [121]. The safety of platelet transfusion in STEC-HUS is still uncertain, with mixed data in the literature, but it may be reasonable in patients with evidence of active bleeding or those who are undergoing a surgical procedure, and risks and benefits must be weighed before any decision to proceed with transfusion.

Intravascular volume must be considered with administration of blood products as well, and patients may benefit from diuretics during or following transfusion, though not all will respond [121].

Disease-specific Therapy

STEC-HUS

Prevention

STEC-HUS, unlike other TMAs, has a characteristic antecedent illness of bloody diarrhea. Recognition of this prodromal phase offers clinicians the opportunity to implement preventative measures to reduce the risk of progression to HUS.

IV Hydration

In patients presenting during the diarrheal phase of enterohemorrhagic *Escherichia coli* (EHEC) illness, provision of IV fluids may reduce the risk of subsequent HUS [123]. A recent meta-analysis established an association between lack of fluid administration and higher hematocrit (>23%) at onset of diarrheal illness with poor outcomes including oligoanuria, need for renal replacement therapy, and death [124].

The role of volume expansion even after onset of HUS has also been explored. In a multicentre surveillance program of children with STEC-HUS, early IV volume expansion was associated with significantly better short-term and long-term outcomes compared to historical controls, including a lower rate of CNS involvement. Restoration of the circulating volume was hypothesized to reduce the formation of thrombi and limit hypoxic ischemic injury [125].

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IV volume expansion should therefore be undertaken for patients presenting with STEC-HUS, and should be considered as well for patients presenting with established HUS early in their illness. However, careful monitoring of urine output and total fluid balance is paramount as fluid therapy will need frequent reassessment, particularly in patients who progress to oligoanuria [126].

Antibiotics

There have been mixed results in the literature as to whether use of antibiotics in STEC illness increases the risk of progression to HUS. The available evidence would suggest that providers should limit the use of antibiotics to patients in whom there is a suspicion of sepsis or severe bacterial illness wherein the risks of potentially increasing likelihood of progression to HUS are outweighed by the benefits of infection control [126, 127].

Management

In addition to the supportive management of AKI detailed previously, other modalities have been investigated for their therapeutic potential in STEC-HUS.

Erythropoietin

Erythropoietin (EPO) has been investigated as a potential option to reduce the need for red blood cell transfusion in patients with HUS in small pediatric studies [128]. At this time there is insufficient evidence to recommend EPO as a standard therapy for patients with HUS.

Plasma Infusion and Plasmapheresis

The American Society for Apheresis (ASFA) lists PE as a recommended therapy for STEC-HUS [129], though this treatment plan may not be any more efficacious than supportive care [130–132].

Dialysis

With progression to anuric renal failure, approximately two-thirds of patients with STEC-HUS ultimately require renal replacement therapy [121]. Both hemodialysis and peritoneal dialysis may be used, and evidence for superior outcomes with one modality versus the other is limited.

Renal transplantation is rarely required in STEC HUS, though when necessary the risk of disease recurrence is minimal [133].

Emerging Therapy and Future Perspectives

Eculizumab

While terminal complement blockade is the mainstay of therapy for complement-mediated TMA (as described below), the use of the monoclonal antibody eculizumab in STEC-HUS is being further elucidated. As detailed previously, greater understanding of the mechanism of STEC-HUS has implicated complement dysregulation in the pathogenesis.

Support for use of eculizumab in STEC-HUS was provided in a case series of three children with severe STEC-HUS with neurologic involvement and dialysis-dependent AKI. Administration of eculizumab was associated with a rapid clinical improvement in all three patients [134]. In 2011, during the *E. coli* O104 outbreak in Germany and France, eculizumab was used in more than 250 patients. The patients treated with the drug had a more severe renal injury and more frequent neurological complications at baseline compared to those who were not treated, and outcomes were similar in both groups. This may suggest a lack of drug effect or may be interpreted as treatment benefit as the group treated with eculizumab may have progressed toward worse outcomes [135]. Since then additional case series reported a significant improvement in neurological function in children with STEC-HUS and neurological impairment treated with eculizumab [136, 137]. Of note, renal impairment persisted in most of these patients [138]. While data for eculizumab in STEC-HUS is limited to observational studies, it may be reasonable to consider this drug for patients with severe disease, particularly with neurologic involvement and when standard therapy has failed.

Shiga Toxin Neutralizing Agents

In an attempt to reduce the pathogenicity of the Stx, oral Stx-binding agents have been developed [139], though to date no such agents (either oral or intravenous) have been proven efficacious in human studies and therefore toxin binding agents are not a standard component of STEC diarrheal illness management [121, 140].

Controversy

While supportive management and AKI therapy are well established in STEC-HUS, the questions surrounding early therapy remain. It appears reasonable to trial volume expansion early in the illness course, with careful monitoring. The role of antibiotics has conflicting evidence, though weighing risks and benefits, avoidance in patients with a low risk of sepsis is favored. Eculizumab as a therapy in STEC-HUS is currently under investigation in larger studies. Until these and future analyses can provide more information, we would consider the use of eculizumab in patients with severe STEC-HUS who are not responding to conventional therapy.

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Complement-Mediated TMA (aHUS)

Plasma Therapy

Therapeutic PE has previously been recommended as early therapy for complement-mediated TMA [141]. Further analysis of outcomes has revealed that there is limited efficacy only on renal prognosis in patients treated with plasma therapy compared to those who were not [142]. In the era of complement blockade, the importance of plasma therapy has diminished.

Eculizumab

For patients with complement-mediated TMA, terminal complement blockade is the therapeutic option of choice. Eculizumab is a humanized monoclonal antibody that binds the complement protein C5 and prevents production of the proinflammatory anaphylatoxin C5a and the product of the terminal complement cascade C5b-9 [118].

In two prospective phase two trials, eculizumab inhibited TMA in patients with complement-mediated TMA and resulted in a significant improvement in renal function [118]. A follow-up analysis demonstrated that these benefits were maintained after 2 years, with no new safety concerns surrounding the therapy [117, 143]. The safety of eculizumab has been demonstrated in further analyses, wherein the most common adverse effects attributed to the drug were fever, and mild gastrointestinal and respiratory symptoms. No deaths of meningococcal infections were noted as patients were systematically vaccinated (Neisseria meningitidis strains A, C, W, Y, and B, *S. pneumoniae*, *Haemophilus influenzae*) and subjected to long-term antibiotic prophylaxis [14, 144].

Eculizumab, when available, should be initiated within 24–48 hours of onset of disease or admission. In children who have been initiated on plasma therapy as a first-line treatment, a switch to eculizumab should be done as soon as the diagnosis of complement-mediated TMA is made [14, 114]. In autoimmune complement-mediated TMA (e.g. CFH) eculizumab is successful in stabilizing patients in the acute phase, though chronic management should target suppression of disease-causing antibodies. When successful, eculizumab may be discontinued in these patients, who may require long-term immunosuppression [5, 145, 146].

Monitoring of complement activity or eculizumab drug levels may be helpful between doses of the drug, as dose adjustments may be considered if there are signs of insufficient blockade. In the long-term management of patients on eculizumab, routine complement activity monitoring may be unnecessary unless there are concerns for clinical status changes (such as infection, trauma, or other triggers) or relapse [125]. Total complement activity (CH50) may be followed. Of note, the normal range of CH50 may vary depending on individual laboratory assays [5].

Dialysis

As with STEC-HUS, many patients with complement-mediated TMA may require dialysis [142]. Patients may be treated with either hemodialysis or peritoneal dialysis, and to date there is insufficient evidence to recommend on modality over the others. Prospective studies of treatment with eculizumab suggest that it may decrease dialysis dependence [118].

Kidney Transplantation

Before the availability of C5-blockade, post-transplant recurrence of complement-mediated TMA was 60%, with 5-year graft survival of 30% in those patients [147].

For individuals with complement-mediated TMA secondary to a mutation in the gene for a circulating complement regulators (such as CFH, CFI, CFB, or C3), liver transplantation has been used as a means of providing a new source of circulating factor production. Liver-kidney transplant has been used as a viable option to maintain graft function before the advent of terminal complement blockade therapy [147–151].

In patients with complement-mediated TMA at high risk of disease recurrence post-transplant and for those who experience recurrence, eculizumab has also been shown to induce remission and graft function recovery [147, 152–154].

In an observational study of 13 renal transplant recipients who were given eculizumab for post-transplant recurrence of complement-mediated TMA, complete reversal of the disease was seen in all patients. Of note, a delay in initiation of anti-C5 therapy was associated with a low degree of renal functional improvement [152]. Eculizumab therapy is promising for both prevention and cure of recurrent complement-mediated TMA in renal transplant recipients [155].

Treatment Duration

The optimal length of therapy for complement-mediated TMA has yet to be determined. Published literature suggests that different underlying mutations may warrant individualized regimens, as the recurrence risk of the disease may vary with the genetic defect [120]. Tools for monitoring complement activity to help guide eculizumab dosing frequency have had some success in smaller cohorts [156] though no large-scale validation of such tools has yet been completed. Strategies toward restrictive use of eculizumab continue to be studied. Whereas lifelong therapy had previously been advocated, it does appear that withdrawal of the drug, followed by close monitoring for signs of disease recurrence (e.g. hematuria, proteinuria, and hypertension) may be appropriate [157], and prospective studies are needed to provide more insight in this area.

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Controversy

While the management of complement-mediated TMA has been revolutionized with terminal complement blockade, there are many questions that remain. Most notable is the appropriate duration of therapy with eculizumab. At this time more data are needed on individual patient risk profiles, complete with genotype-phenotype correlation. Efforts are ongoing in this field to establish optimal treatment regimens.

Conclusion

TMAs represent a disease spectrum for which our understanding has increased dramatically over the past decade. What was once defined as a TTP/HUS spectrum has now expanded into multiple disease processes with many clinically similarities and distinct features. An increasing body of literature supports the role of complement dysregulation as one of the disease-causing mechanisms in the TMA spectrum. Common to the TMA disease entities are the triad of MAHA, thrombocytopenia, and AKI, and the severity of illness can range from mild disease to severe disease with prolonged sequelae and high mortality.

HUS is an entity under the umbrella of TMA. The most common cause, STEC-HUS, has long been considered as independent of the rest of this spectrum of diseases as it has a defined trigger and known secondary cause of microangiopathy. However, it has more recently been discovered that much like in other TMA, complement dysregulation may play a prominent role in the pathophysiology as well.

In complement-mediated TMA the importance of the complement cascade in disease progression has led to a revolution in therapy with the advent of eculizumab, a form of terminal pathway blockade. Since the introduction of this drug, disease remission has become attainable and mortality has improved considerably. Understanding the role of complement in TMA has led to the use of eculizumab in select cases of STEC-HUS as well, and its role in the management of this entity continues to be elucidated.

While complement pathway blockade has offered the prospect of improved outcomes, questions remain to be answered regarding the optimal dosing or duration of therapy. In STEC HUS, the notion of preventative management or neutralizing toxins has thus far not shown any benefit in clinical studies, though investigations are ongoing. In complement-mediated TMA, although many mutations have been defined, others continue to be discovered. The significance and therapeutic potential of these mutations is still unknown and further study in genetics will hopefully help to inform future clinical trials in this area.

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Pregnancy

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Introduction

Major physiological adaptive changes to renal hemodynamics, and glomerular and tubular function occurs with pregnancy. Normal physiological adaptations leading to hyperfiltration in pregnancy are not pathogenic in women with normal kidneys, but may unmask underlying chronic kidney disease (CKD) for the first time or contribute to worsening of existing CKD. This may manifest as temporary or permanent loss of renal function, and adverse pregnancy outcomes. Therefore pregnancy is an important challenge to the maternal kidney.

This chapter primarily discusses pregnancy in women with CKD at all stages. Clinical decision-making in this high-risk cohort is focused mainly on risk assessment for maternal and fetal outcomes, with very limited evidence regarding interventions. Appraisal of the literature is hampered by the quality of existing data, and there are large knowledge gaps regarding best clinical practice. Observational studies of small, often heterogeneous, and usually retrospectively studied cohorts may not be readily compared. Definitions of CKD differ between studies and over time, with the widespread introduction of CKD staging highlighting the outcomes of pregnancy with less severe CKD. Registry and population cohort studies have illuminated outcomes but often lack detailed clinical data for more complex analysis of risks and outcomes.

Maternal (obstetric and renal) and perinatal outcomes worsen as preconception estimated glomerular filtration rate (eGFR) declines. Hypertensive disorders of pregnancy often drive premature delivery and thereby define fetal outcomes. Management approaches are usually extrapolated from other cohorts at risk of preeclampsia or those with chronic hypertension. Over time, there has been growing confidence in supporting pregnancies in women with kidney disease, even those receiving dialysis, and for women after kidney transplantation. It is no longer routine practice to advise against pregnancy in these women.

Parenthood remains an important goal, but the desire for motherhood is balanced with fears of compromising their own and their child's health. Approaches to care involve understanding the patient's experiences and values whilst acknowledging medical risks. Key management points relate to meticulous preconception planning, informed shared decision-making about the options, and timing and management of pregnancy based on individualized assessment of risks. The involvement of multidisciplinary expert teams, and careful maternal and fetal surveillance throughout pregnancy are essential.

Epidemiology

Chronic Kidney Disease

Defining CKD in pregnant women is challenging, especially where preconception kidney function is unknown – this is common given that assessment of kidney function is not routine in pregnancy. Robust prevalence data is lacking for many populations, with significant heterogeneity between studies that often have small numbers. Definitions vary, data is often historical, and clinical care practices may differ between centers and change over time. In population pregnancy datasets, kidney data is poorly captured, whereas renal registry datasets lack detailed pregnancy data. In all cohorts, early pregnancy loss is difficult to capture and likely underestimated. These factors limit comparison and risk quantification [1], and

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should be considered when interpreting studies and when synthesizing data from different studies.

The largest study identifying CKD in pregnancy was a Norwegian population-based data linkage study of 5655 births from 3405 women, assessing eGFR by the Modification of Diet in Renal Disease (MDRD) formula. This study found CKD in 3.3% of pregnancies, with 2.4% with stage 1, 0.8% with stage 2, and 0.1% with stage 3 [2]. This data may be extrapolated to similar countries, but the true prevalence of CKD in most pregnant cohorts remains unknown.

Dialysis

The number of pregnancies in patients receiving dialysis reported in the literature is increasing over time, although they remain rare [3, 4]. Absolute pregnancy rates are difficult to define and compare. The Australian and New Zealand Dialysis and Transplant Registry (ANZDATA) has reported the pregnancy rate in chronic hemodialysis patients was 8.4/1000 patient-years between 2001 and 2011, with a live birth rate of 1.26/1000 patient-years [5]. Comprehensive survey data from Belgium reported a conception rate of 0.3/1000 patient-years, and a study from Japan showed 3.4% of women of childbearing age conceived [6–8]. An Italian study found that a live birth rate was 0.7–1.1 per 1000 women per year compared to the national rate of 72.5 per 1000 women per year [9]. These data suggest that the birth rate in patients on peritoneal dialysis (PD) is lower than that in hemodialysis recipients [3–5]. The reasons for this are uncertain, but may be due to hypertonic fluid disrupting implantation or causing adhesions [10], or change in dialysis modality to prior to conception [5].

Transplantation

Since the first successful birth post renal transplantation in 1958, the rate of conception and numbers of live births post kidney transplantation have continued to increase [11]. The ANZDATA registry has reported a rate of 20/1000 patient years from 1996 to 2005 with a live birth rate of 16/1000 patient-years [4, 11]. The United States Renal Data System registry reported a pregnancy rate of 33/1000 patient-years [12]. The UK Obstetric Surveillance Study recognized all pregnancies in renal transplant recipients, with a rate of 7.6/1000 patient-years [13]. Italian data revealed a birth rate of 5.5–8.3 per 1000 women [14]. The impact of widespread use of mycophenolate mofetil immunosuppression on pregnancy rates in patients with transplant or glomerulonephritis in the recent era of care is yet to be determined.

Acute Kidney Injury

The epidemiology of acute kidney injury (AKI) in pregnancy depends on the geographical location and definition used, and the literature is highly variable. AKI diagnosis based on rise in serum creatinine (absolute value >90 μmol/l, doubling of serum creatinine) is likely more common but poorly captured in studies. In the developed world, AKI is uncommon and predominantly due to volume loss or hypertensive disorders of pregnancy, and less commonly de novo renal disorders. AKI requiring acute dialysis in pregnancy is rare, occurring in 1 per 10 000 (95% confidence interval [CI] 0.8–1.1) [15]. By contrast, in developing nations AKI is mainly due to sepsis and rates are higher but variable [16].

Pathophysiology

Physiological Changes with Pregnancy

The kidney undergoes marked physiological and structural changes to adapt to the demands of pregnancy, occurring as early as 6 weeks from conception and continuing postpartum (summarized extensively in the paper by Odutayo et al. [17]). These physiological changes are essential adaptions to maintain maternal and fetal health, but previously unidentified kidney disease may be exposed and underlying renal dysfunction may worsen. Systemic hemodynamic changes include vasodilatation mediated by hormones including relaxin and nitric oxide, decreased systemic vascular resistance and increased cardiac output [18]. A nadir in the mean arterial pressure occurs by 18–24 weeks, with subsequent rise in later gestation. Concomitantly, the renin-angiotensin system is activated in pregnancy. Renal tubular changes occur due to complex shifts in hormone responsiveness, with a net increase in total body sodium and potassium, resetting of receptor thresholds for antidiuretic hormone release, and fall in plasma osmolality [17].

All of these factors contribute to expanded plasma volume, increased renal plasma flow (by 50–80%), and increased glomerular hyperfiltration (by 50%) but *without* glomerular hypertension [19]. It is important to note that many physiological studies of pregnancy are historical and lacking contemporaneous data exploring hyperfiltration in mothers who are older or have comorbidities of diabetes and obesity.

Structural changes of the renal tract also occur, with increased kidney size due to expansion of intravascular and interstitial volume. Ureteral and pelvic dilatation is commonly seen, may mimic obstruction, and predisposes to urinary stasis and infection.

Fertility and CKD

Fertility is affected by CKD and declines as renal function worsens. Mechanisms include impaired ovulation due to hormonal dysregulation with hyperprolactinaemia and decrease

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in gonadotropin-releasing and luteinizing hormone pulsatility, decreased ovarian reserve and decrease in libido [20–22]. Women may also be discouraged from conceiving due to concerns for their health [23]. Intensive dialysis may increase the ability for conception [24], but transplantation remains the main mechanism for restoring fertility.

Diagnosis

Markers of Kidney Function in Pregnancy

In normal pregnancy, GFR increment results in greater creatinine clearance and fall in serum creatinine by the second trimester. An accurate estimation of GFR is consequently difficult, with reliance on serum creatinine alone. The gold standard 24 hour urine collection for creatinine or inulin is impractical for clinical use. Commonly used formulae to estimate GFR are not validated in pregnancy. The Cockcroft–Gault formula underestimates GFR compared to inulin clearance and overestimates compared to 24-hour urine creatinine clearance. The MDRD and CKD – EPI formulae underestimate GFR [25–27]. The international classifications of AKI are also not validated in the pregnant population.

Urinary protein excretion increases during pregnancy and can rise until delivery; proteinuria up to 300 mg/24 h may be observed in normal pregnancy [28]. There are multiple contributory mechanisms, including physiological hyperfiltration, reduced tubular protein reabsorption, and increase in glomerular basement membrane pore size. Whilst 24-hour collection is still considered gold standard, the spot protein:creatinine ratio can be used instead for assessing significant proteinuria above 30 mg/mmol and is also validated in hypertensive women [29].

Diagnosing Pregnancy in Patients with CKD

Renal excretion of β-human chorionic gonadotropin (β--HCG) is reduced in renal impairment and thus urine pregnancy tests can be falsely positive [30]. Irregular menstruation is often observed in advanced CKD, and thus serial β-HCG and ultrasound is a better indicator of gestational age than the date of the last menstrual cycle [30]. β-HCG is used in antenatal screening for aneuploidies, which can increase false positives and should be interpreted with caution [31, 32]. Pregnancy-associated plasma protein A (PAPP-A) used in first trimester screening panels is elevated in patients receiving heparin and unpredictable in late-stage CKD [32, 33].

Diagnosing Preeclampsia in Patients with CKD

Differentiating superimposed preeclampsia from worsening CKD due to pregnancy is a diagnostic challenge due to the common features of hypertension, proteinuria, and progressive renal dysfunction [34]. Superimposed preeclampsia with inpatients with underlying CKD contributes to worse outcomes of preterm delivery and small for gestational age. Parameters such as liver function tests and platelet count can assist with differentiation. Systemic lupus erythematosus (SLE) nephritis flares can be difficult to separate from preeclampsia; systemic features of SLE and low complement levels, and elevated double-stranded DNA can aid differentiation [35, 36]. Doppler ultrasound of the umbilical artery to assess changes in waveform and vascular resistance can be useful. Whilst only small studies have been performed, results suggest a high specificity for predicting preeclampsia [34, 37].

Novel biomarkers including soluble fms-like tyrosine kinase (sFlt), placental growth factor (PIGF), and serum placental protein 12 may help in differentiating and predicting preeclampsia in women with CKD [34, 38]. A meta-analysis reviewed use of the sFLT:PIGF ratio as a predictive and diagnostic marker of preeclampsia, and found in both low and high risk patients this could predict development of preeclampsia with a sensitivity of 80%, specificity of 92%, positive likelihood ratio of 10.5, and negative likelihood ratio of 0.22 [39]. Larger cohort studies are needed to clarify the diagnostic benefit of these markers.

Kidney Biopsy

The safety of kidney biopsy in pregnancy is contentious. A systematic review of 197 biopsies showed a complication rate of 7% with the highest risk period being after 25 weeks gestation [40]. It is rarely indicated for differentiation between preeclampsia and primary renal pathology. Biopsy should be undertaken cautiously, preferably in early pregnancy, and only when clinical management is likely to substantially alter based on biopsy results. Otherwise it should be deferred until after delivery. Postpartum kidney biopsy to investigate abnormal renal function or proteinuria commonly identifies pathological glomerular disease [41]. Preconception kidney biopsy may be very informative in assisting with pregnancy planning and risk stratification, especially for transplanted women and those with SLE nephritis.

Prognosis

Impact of Maternal Kidney Disease on Pregnancy Outcomes

There is a substantial body of evidence from cohort and population studies that both maternal and fetal outcomes are worse with any degree of renal dysfunction compared

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to women without CKD, and deteriorate along the continuum of CKD severity [14, 42–46]. The key adverse maternal pregnancy complication is worsening hypertension or preeclampsia, which likely drives preterm delivery and high cesarean section rates. There is increased risk of premature birth, low birth weight, small for gestational age, neonatal intensive care unit admissions, and infant death [3]. Risks are compounded by comorbidities, particularly chronic hypertension and proteinuria (>1 g/day), and some primary diseases [47]. Chronic hypertension is highly prevalent in women with CKD, and alone confers a 7–8-fold relative risk of preeclampsia, which drives other adverse perinatal outcomes [48]. Hypertension is an additive risk for adverse outcome when combined with any stage of CKD [2, 14]. Early-stage CKD may be underrecognized in pregnancy, but also confers an increased risk of pregnancy complications and adverse perinatal outcome compared to women with no CKD, and is not entirely benign [2, 14, 43]. Reassuringly maternal mortality is very rare [3].

Impact of Pregnancy on Kidney Function

The influence of pregnancy on renal outcomes is not always predictable or guaranteed despite best efforts at risk stratification, which makes counseling a challenge. Our understanding of the risk of decline in kidney function with pregnancy in women with CKD has been informed by several cohort studies [14, 46, 49]. A large systematic review showed no difference in renal outcomes between women with or without CKD in pregnancy (Table 27.1). However, this review included few studies in women with advanced CKD who are at greatest risk of declining renal function during and after pregnancy, and evaluated substantial renal decline only [43]. A long-standing cohort study indicated that across all stages of CKD, pregnancy was associated with an increase in hypertension, increase in proteinuria, and worsening of CKD stage postpartum, and the risk increased based on preconception CKD stage [14]. A smaller longitudinal cohort study in later stages of CKD showed proteinuria >1 g/24 h and an eGFR under 40 ml/min/1.73 m^2 predicted decline in eGFR postpartum [46].

Overall, preconception kidney function is an important predictor of risk of decline in kidney function during and after pregnancy, but it must be considered along with other factors such as hypertension, proteinuria as an indicator of chronic damage or primary disease activity and renal biopsy information. In addition, antenatal complications such as infection, preeclampsia and hypovolaemia may cause an AKI, which can also have an impact on longer-term outcomes.

Primary Disease and Pregnancy Outcomes

The impact of primary renal disease varies depending on the specific disease and the severity of kidney dysfunction (which may not always be reported or comparable between studies). The most robust data exists for IgA nephropathy, where the preconception kidney function, proteinuria, and hypertension are the key prognostic factors [53, 57]. There is little data on other glomerular diseases and pregnancy. An exception is SLE nephritis, where clear evidence suggests maternal and fetal outcomes are worse irrespective of renal function, particularly with antiphospholipid syndrome or active renal disease [35, 47]. Active disease pre conception and during pregnancy is associated with increased maternal and fetal morbidity [35, 36, 47, 58]. A meta-analysis of outcomes of pregnancy with SLE nephritis (Table 27.1) found increased risk of SLE flares, hypertension, preeclampsia, premature birth, and low birth weight, particularly in women with active SLE nephritis [47]. Diabetic nephropathy is also an additive risk factor for worse outcomes for both type 1 and type 2 diabetic women who already have higher rates of pregnancy complications [54, 59, 60]. There may be an increased risk of congenital malformations with diabetic nephropathy above that of poorly controlled diabetes alone [61].

Pregnancy and Dialysis

Pregnancies in the hemodialysis population have historically had poor outcomes. Since the 1990s, with better perinatal care and understanding of the importance of intensive dialysis, outcomes have improved, with increased live birth rates of 70–80% [4]. However, pregnancies in chronically dialysed women remain complicated by maternal hypertension (50–70%), preeclampsia (18–67%), polyhydramnios (up to 40%), intrauterine growth restriction (17–77%), and prematurity and low birth weight (50–100%) [3–5, 62]. Compared to transplanted patients, patients receiving hemodialysis have a higher rate of growth restriction, placental abruption, blood transfusion, and intrauterine death [63]. Enhanced clearance of urea and other molecules through intensified dialysis regimens (at minimum >20 hours per week) has beneficial effects on fetal mortality, birth weight, and gestational age, and is especially relevant in women with minimal residual renal function [62]. The presence of residual renal function, particularly being nondialysis dependent at time of conception, leads to higher live birth rates (up to 90% for pregnancies reaching 20 weeks of gestation) compared to those who conceive once established on hemodialysis with less residual function [5, 64]. No studies have assessed the level of renal function at which

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Table 27.1 Summary of selected systematic reviews relevant to kidney function assessment, pregnancy in women with kidney disease, and transplants.

Author (year)	Title	Search period	Studies	Patients (pregnancies)	Inclusion criteria	Analysis method	Data quality (as per reviewers)	Key findings
Diagnosis and management								
Cote, et al. (2008) [29]	Diagnostic accuracy of urinary spot protein:creatinine ratio for proteinuria in hypertensive pregnant women: systematic review	1980–2007	13	1241	Studies that compared urinary protein creatinine ratio or albumin creatinine ratio with urine protein excretion over 24 h in pregnant women with hypertension	Quality Assessment of Diagnostic Accuracy Studies tool for assessing validity; diagnostic meta-analysis	Minimal study heterogeneity. Studies inadequately described selection criteria, disease spectrum and test execution.	Spot PCR can exclude proteinuria of >0.3 g/day in hypertensive women. Sensitivity 83.6%; specificity 76.3%; positive likelihood ratio 3.53; negative likelihood ratio 0.21.
Piccoli et al. (2013) [40]	Kidney biopsy in pregnancy: evidence for counseling? A systematic narrative review	1980–2010	39	243 biopsies in pregnancy; 1236 post	Studies on kidney biopsy in pregnancy with >5 patients. Excluded renal transplant	Narrative synthesis	Heterogeneous cohorts; only narrative review possible	Higher complication rate for renal biopsies in pregnancy compared to postpartum (7% vs.1%). Biopsy led to therapeutic changes in 66% of cases.
Tong et al. (2015) [50]	Perspectives on pregnancy in women with chronic kidney disease: systematic review of qualitative studies	To April 2014	15	257	Qualitative studies on experiences of adult women with pregnancy and CKD	The Enhancing transparency in reporting the synthesis of qualitative research framework; thematic synthesis	The review was limited by study cohort heterogeneity. Pregnancy was not always the major focus of the study.	Seven themes identified: pursuing motherhood, failure to fulfill social norms, fear of birth defects, exacerbating disease, decisional insecurity and conflict, control and determination, withholding emotional investment.
Transplantation								
Bar et al. (2001) [51]	Pregnancy outcome after cyclosporine therapy during pregnancy: a meta-analysis	NA	15	410	Studies reporting congenital malformations with babies exposure to cyclosporine, with >10 patients	Meta-analysis	Definition of malformation varied. Studies were at risk of publication and selection bias.	Overall prevalence of malformations with cyclosporine exposure was similar to the background rate in the general population.
Deshpande et al. (2011) [52]	Pregnancy outcomes in kidney transplant recipients: a systematic review and meta-analysis	2000–2010	50	3570 (4706)	Studies on pregnancy, obstetric, delivery complications in kidney transplant recipients Case reports, abstracts and articles not in English were excluded	Meta-analysis	Potential patient overlap between studies (repeated inclusion). Definitions and classification of key outcomes varied between studies. Reporting and selection bias was likely due to voluntary reporting.	Live birth rate was higher and miscarriage rate was lower than the general population (possibly due to bias). Preeclampsia, gestational diabetes, preterm delivery, and cesarean section were higher than the general population. Hypertension, proteinuria and elevated serum creatinine were associated with adverse outcomes.

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Dialysis								
Piccoli et al. (2016) [3]	Pregnancy in dialysis patients in the new millennium: a systematic review and meta-regression analysis correlating dialysis schedules and pregnancy outcomes	January 2000–December 2014	126	647 (681)	Studies on pregnancy in chronic dialysis patients who started dialysis in the first 20 weeks of gestation; gestation >24 weeks; with >4 patients	Meta-analysis	Study cohorts were heterogeneous. Historical studies were excluded.	Fewer hours of dialysis per week was associated with preterm deliveries, small for gestational age births. Lower incidence of small for gestational age babies in hemodialysis compared to peritoneal dialysis.
Piccoli et al. (2010) [40]	Pregnancy in dialysis patients: is the evidence strong enough to lead us to change our counseling policy	2000–2008	10	78 (90)	Studies of pregnancy in dialysis with >5 patients	Descriptive narrative review	Studies had varied definition of outcomes and study period with high heterogeneity and low numbers.	Intrauterine death, polyhydramnios, preterm delivery and small for gestational age were prevalent in dialysed women. Possibility of a healthy child was 50–100%.
Chronic kidney disease								
Bramham et al. (2014) [48]	Chronic hypertension and pregnancy outcomes: systematic review and meta-analysis	To June 2013	55	(795 221 pregnancies)	Studies of pregnant women with chronic hypertension excluding women with superimposed preeclampsia with >20 women	Preferred Reporting Items for Systematic Reviews and Meta-Analyses, guidelines; Newcastle-Ottawa scale for grading; meta-analysis	Study cohorts were heterogeneous.	Women with hypertension in pregnancy had a high incidence of preeclampsia, cesarean section, preterm delivery, low birth weight, intensive care unit, admission and perinatal death.
Nevis et al. (2011) [45]	Pregnancy outcomes in women with chronic kidney disease: a systematic review	To June 2010	13	Cases 2682, controls 26 149	Studies that reported fetal or maternal outcomes in women with CKD with small size >5, dialysis and transplant patients were excluded	Descriptive review and meta-analysis	Confounding factors were adjusted in analyses in only six studies. Studies were often small and retrospective, with a risk of selection, ascertainment, surveillance and misclassification bias.	The risk of adverse fetal outcomes of premature birth, small for gestational age, intrauterine growth restriction, low birth weight and stillbirth were two times higher in women with any CKD. Due to study limitations, definitive risks for women with CKD are not able to be quoted on the basis of this literature.
Zhang et al. (2015) [43]	A systematic review and meta-analysis of outcomes of pregnancy in CKD and CKD outcomes in pregnancy	1946–2014	23	(506 340)	Cohort and case control studies of women with CKD and maternal or fetal outcomes, and with a non-CKD control group. Studies of women with a history of autoimmune disease, on maintenance HD, kidney transplant, or acute kidney injury were excluded.	GRADE system for assessing study quality; meta-analysis	The outcomes of preeclampsia and premature delivery had high-grade evidence quality. The other outcomes were very low grade due to heterogeneity. Studies included had few women with renal impairment.	Pregnancy in women with CKD had a greater risk of preeclampsia, premature delivery, small for gestational age and cesarean section. Proteinuria was a risk factor for preeclampsia and preterm delivery. Pregnancy was not a risk factor for progression of kidney disease, but included patients had mainly early-stage CKD.

(*Continued*)

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Table 27.1 (Continued)

Author (year)	Title	Search period	Studies	Patients (pregnancies)	Inclusion criteria	Analysis method	Data quality (as per reviewers)	Key findings
Blom et al. (2017) [53]	Pregnancy and glomerular disease: a systematic review of the literature with management guidelines	1980–February 2016	18	887 (1414)	Studies on frequency of live births of women with biopsy proven glomerulonephritis with >10 cases	Narrative review	Significant study heterogeneity which precluded pooling of data thus review was narrative.	Regardless of etiology of glomerular disease, increased proteinuria, hypertension or renal dysfunction were associated with worse pregnancy outcomes
Piccoli et al. (2013) [54]	Type 1 diabetes, diabetic nephropathy, and pregnancy: a systematic review and meta-study	1980–2012	35	(1 511)	Studies on pregnancy outcomes in women with type 1 diabetes and nephropathy with <5 sample size	Narrative review	Studies were highly heterogeneous and only narrative review was possible.	The evidence on pregnancy outcomes in diabetic nephropathy in scarce. The risks of adverse pregnancy events are high and have not changed over time. Stillbirth and fetal death are in increased in diabetic nephropathy compared to other primary disease.
Piccoli et al. (2018) [12]	A systematic review on the materno-fetal outcomes in pregnant women with IgA nephropathy: A case of "late maternal" preeclampsia	2000–April 2017	27	581 (729) control 562	Case reports or case series that reported on pregnancy outcome or renal function in women with IgA nephropathy	Meta-analysis	There was heterogeneity in terms of definitions, populations, outcomes and follow up duration. Meta-analysis was conducted. Most studies had women with normal kidney function.	No increased risk in progression of kidney disease in women with IgA who had pregnancy vs. no pregnancy. Adverse pregnancy outcomes were increased compared to healthy controls – 10× increased risk of preeclampsia and hypertension. Preterm birth and risk of low birth weight babies was increased to a lesser degree. Authors hypothesized that late preeclampsia may have less impact on fetal outcomes.
Liu et al. (2016) [55]	A systematic review and meta-analysis of kidney and pregnancy outcomes in IgA nephropathy	1966–2015	4	273 (376) vs. 241 IgA without pregnancy	Cohort or case control studies of patients with biopsy proven IgA on pregnancy outcomes	GRADE criteria to assess study quality; meta-analysis	Moderate quality evidence. No evidence of publication bias.	No increase in the risk of adverse renal outcomes compared to IgA nephropathy without pregnancy. There were high rates of preeclampsia, infant loss, preterm delivery and low birth weight.
Smyth et al. (2010) [47]	A systematic review and meta-analysis of pregnancy outcomes in patients with SLE and SLE nephritis	1966–2009	37	1 842 (2 751)	Studies of pregnancy outcomes with at least 1 month of follow-up	Cochrane search strategy; meta-analysis	Studies are mainly observational and subject to reporting and selection bias.	Controlling SLE activity prior to conception is important as active SLE nephritis and antiphospholipid antibodies increase the risk of maternal hypertension and poor fetal outcomes.
Wu et al. (2018) [56]	Management and outcomes of pregnancy with or without lupus nephritis: a systematic review and meta-analysis	2000–June 2017	16	1760	Cohort or cross sectional studies comparing Pregnant women with SLE without nephritis vs. without nephritis	Newcastle–Ottawa Scale and Strengthening the Reporting of Observational Studies in Epidemiology checklist to assess study quality; meta-analysis	Statistical heterogeneity was seen across the studies.	Worse maternal and fetal outcomes were seen with SLE nephritis. Anti- Ro antibodies had worse outcome. More immunosuppression was used in SLE nephritis.

Reviews relating to pregnancy in non-CKD or mixed cohorts are not included due to space constraints. Analysis methodology describes systems used for grading quality of studies (if done), and broad method of data synthesis (narrative, thematic or meta-analysis).

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dialysis should be commenced to optimize pregnancy outcomes or the impact of commencement of dialysis for fetal indications on maternal renal survival.

There is less data on pregnancy in peritoneal dialysis recipients, which remains very rare [3, 5]. Successful pregnancy outcomes have been observed in women receiving PD throughout pregnancy, but peritonitis remains the main concern [65]. Most women are switched to hemodialysis [5], and there is some data suggesting fetal outcomes are better with peritoneal dialysis than haemodialysis [3].

Pregnancy Outcomes after Kidney Transplantation

Transplantation restores fertility and offers an opportunity to achieve parenthood with less risk than in dialysed women. In the recent era, elective termination rates have fallen and transplanted women are very likely to have a live birth (overall live birth rates of 76–98% in pregnancies reaching 20 weeks gestation) [66, 67]. Compared to patients receiving dialysis, the maternal and fetal outcomes post transplant are superior, though the rate of conception remains lower than in the general population [9, 63]. However, obstetric complications remain high, with increased risk of gestational hypertension, preeclampsia (seen in 25–35% of pregnancies), growth restriction, and preterm birth (in 30–50%) [52, 63, 68, 69]. Australian registry analysis demonstrated a mean difference in gestational age of 3.5 weeks, gestational weight of 873 g, and lower perinatal survival for babies born to transplanted mothers compared to the general population [66]. Higher gestational diabetes rates have been reported in some studies [52], but not consistently [66, 68]. A transplantation-to-conception interval of under 2 years has been associated with higher rates of gestation diabetes, preeclampsia, and cesarean section [52]. Similar to the CKD cohort, preconception kidney function and chronic hypertension are predictive of adverse obstetric outcomes, particularly preeclampsia [52, 68–71]. Majak et al. reported the risk of preeclampsia increased in women with chronic hypertension, previous preeclampsia or preconception serum creatinine ≥125 μmol/l. The effect of each risk factor was cumulative, and those with all three factors had a 96% risk of preeclampsia [72]. Immunosuppression exposure, infections, and diabetes may influence outcomes but the data defining this are limited. Despite longer immunosuppression exposure, women who are transplanted in childhood have similar outcomes in pregnancy to those transplanted in adulthood [67].

Impact of Pregnancy on Transplant Outcomes

Several registry and cohort studies have reported that graft and patient failure is not accelerated by pregnancy, although it is worth noting that 30–40% of women will have graft failure by their child's 10th birthday and 10–20% will not live to see their child into adulthood [11, 69, 70, 73]. Pregnancy is less likely to adversely impact graft outcomes in women with normal and stable allograft function. There is growing data demonstrating that preconception graft function predicts long-term graft function after pregnancy [67, 68, 70–72]. In one cohort study where detailed kidney function data was available at multiple time-points, the risk of decline in graft function during pregnancy and at 12 months postpartum was increased as preconception creatinine declined. Women with serum creatinine >140 μmol/l had worse renal trajectory and risk of graft loss [68]. Preeclampsia can increase the risk of temporary decline in kidney function but has not been shown to impact adversely on longer term graft outcome [72]. Time from transplant to pregnancy may also influence outcomes, with one large US study suggesting pregnancies within 3 years post transplantation were associated with poorer survival [74] but this was not consistently demonstrated in other cohorts [11, 66].

The longer-term impact of immunosuppression modification, particularly cessation of mycophenolic acid derivatives, for facilitation of pregnancy remains unknown. Episodes of acute rejection in pregnancy are reassuringly low (2–14.5%) and no higher than in the nonpregnant population [52, 69, 73, 75–77]. This could be under-reported as biopsy may selectively be avoided during pregnancy. De novo allo-sensitization is frequent after nontransplant pregnancy, but only reported in 6% of transplanted women, presumably due to immunosuppression use [78].

Treatment

Prepregnancy Counseling and Planning

Parenthood should be discussed early to determine the optimal "window" for conception based on an individual's life plan and clinical situation. There is increasing support for women with CKD or transplants in pursuing motherhood, and clinical practice guidelines no longer advise against pregnancy but encourage counseling with individual risk stratification based on relevant comorbidities. Given the morbidity associated with pregnancy, careful planning is essential with effective contraception in place. This provides the opportunity to optimize health and risk factors for adverse outcomes and adjust medications. In addition, clinicians can obtain multidisciplinary assessment, engage additional expertise, for example preimplantation genetic testing for inherited diseases, assess fertility and confirm the best timing of pregnancy [79, 80].

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Navigating pregnancy can be emotionally daunting for women with CKD or transplants. Counseling should incorporate shared decision-making, which involves understanding patient values and perspectives, balancing the emotional vulnerabilities, while sensitively acknowledging the medical risks [23]. Women with CKD have described the need to balance social expectations and their strong desire for motherhood with fears regarding disease exacerbation, their own survival, and fetal harm. Explanation of medical risk should avoid catastrophizing and be balanced with a women's values of autonomy and family, focusing on shared decision-making and provision of hope [23, 81]. In a retrospective study of women managed in a specialized multidisciplinary preconception counseling clinic for CKD, 92% found expert counseling useful in assisting with decision-making [80]. Risk stratification based on key factors associated with adverse pregnancy outcome can identify areas where maternal health may be optimized (Table 27.2).

Optimize Maternal Health Pre Conception

Women planning pregnancy should cease smoking, commence folic acid and vitamins, exchange teratogenic medications for pregnancy-safe options, and address relevant comorbidities including infection, anemia, and diabetes. Primary renal disease should be controlled or in remission, and transplant function and immunological parameters should be stable. Assessment of renal status should include abiopsy if necessary to clarify diagnosis, disease activity or exclude subclinical rejection. Optimization of glycaemic control in patients with diabetes can reduce maternal and fetal adverse outcomes [59]. Vesicoureteric reflux and polycystic kidney disease confer increased risk of urinary tract infections [90]. Symptomatic urinary tract infections and asymptomatic bacteriuria are associated with maternal sepsis as well as preterm birth and low birth weight and should be treated aggressively [91].

Table 27.2 Recommendations for treatment and management of women with CKD in pregnancy.

Treatment	Recommendation	Certainty of evidence	Strength of recommendation
Preconception counseling	We recommend expert pre conception counseling be undertaken early to enable shared decision making about parenthood options for women with CKD	Moderate	Strong [23, 50, 80, 81]
Risk assessment	We recommend using pre-conception kidney function as the primary parameter for assessing risk of adverse pregnancy and renal outcomes	Moderate	Strong [43, 45]
Cessation of mycophenolate mofetil and Mycophenolic acid	We suggest MMF or MPA be ceased at least 3 months prior to conception due to embryotoxicity	Moderate	Strong [82, 83]
Cessation of ACEI or ARB	We suggest in continuing ACEI/ARB until conception in selected women, where the benefit of controlling proteinuria may outweigh fetal risks from early first trimester exposure	Very low	Weak [48, 84, 85]
Controlling hypertension	We suggest controlling hypertension prior to conception and during pregnancy Aiming for a target blood pressure of 140/90 may reduce episodes of severe hypertension in pregnancy and does not adversely affect the fetus	Moderate	Strong [2, 46, 86]
Prophylactic aspirin	We suggest women at high risk of preeclampsia with CKD, kidney transplant, hypertension or SLE as their primary disease take prophylactic low-dose aspirin from the first trimester for preeclampsia prevention	Very low (in CKD population); moderate-strong in general pregnancy cohorts	Strong [87, 88]
Intensive dialysis	We suggest that dialysis delivery be intensified in pregnant women receiving renal replacement therapy, tailored to residual renal function More than 20 and up to 36 h per week should be considered in women with no residual function, but must be balanced with what can be tolerated and accommodated	Low–moderate	Strong [40, 46, 89]

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SLE nephritis should be quiescent 6 months prior to conception to minimize risk of disease flare and improve odds of pregnancy success [35, 47]. Hydroxychloroquine should be continued during pregnancy as cessation is a risk factor for disease flare and continuation improves fetal outcome [58, 92, 93]. A meta-analysis of hydroxychloroquine use found no increase in rate of congenital malformation but observed more spontaneous abortion, possibly from indication bias related to underlying disease activity [94]. All patients with SLE should be screened for antiphospholipid antibodies as they portend a worse prognosis [35, 36, 47]. Antiphospholipid syndrome with thrombosis should be treated with anticoagulation. Screening for anti-Ro and anti-La antibodies should occur to identify those at risk of neonatal cardiac SLE, particularly given hydroxychloroquine can reduce this risk [35, 95–97].

Hypertension

Controlling hypertension before and during pregnancy is essential. There is insufficient evidence for blood pressure targets in pregnancy with CKD, though consensus guidelines recommend a target of <140/90 [98–100]. The CHIPS trial showed tighter control of blood pressure reduced episodes of maternal hypertension over 160/110 mmHg without adverse fetal outcomes, but this has not been studied in CKD populations [86, 101]. Antihypertensive therapy should be changed to pregnancy-safe drugs such as labetalol, methyldopa, and nifedipine, but there are no data to guide choice of one agent over another [13, 79]. Angiotensin receptor blockers (ARB) and angiotensin converting enzymes inhibitors (ACEI) are contraindicated beyond the first trimester due to risk of renal dysplasia, oligohydramnios, neonatal renal failure, and fetal death [102]. More recent population studies suggest hypertension and underlying comorbidities may be teratogenic rather than ACEI or ARB themselves [48, 84, 85]. Continued stabilization of proteinuria with these drugs, with careful surveillance for pregnancy, may be recommended in selected women where the risk of prolonged cessation of renin-angiotensin blockade outweighs the potential fetal risk from exposure at conception [103].

Pregnancy Management: General Principles

Once pregnant, multidisciplinary antenatal care and a tailored plan for maternal and fetal surveillance should be established based on CKD stage, comorbidity, and transplant status (Figure 27.1) [79]. Careful vigilance should occur for declining maternal renal health, superimposed preeclampsia, fetal growth restriction, polyhydramnios, and infection, as these events will define timing of delivery.

Women should commence low-dose aspirin (75–100 mg daily) before 12 weeks and continue until late in the third trimester. Reduction in preeclampsia risk due to aspirin has been demonstrated in low-risk [101] and high-risk populations [87, 104]. A meta-analysis that included moderate- to high-risk patients, including those with CKD and hypertension, confirmed a risk reduction of 0.47 (95% CI 0.36–0.62) vs. 0.78 (95% CI 0.61–0.99; $P < 0.01$), if commenced prior to 16 weeks gestation [88]. These conclusions have been extrapolated to patients with CKD and incorporated into guidelines [72, 99, 105].

Given pregnancy is a prothrombotic state, women with nephrotic range proteinuria should be considered for prophylactic anticoagulation [79], although there are negligible outcomes data. Nutrition should be evaluated and supplementation provided as required. Gestational diabetes screening should occur earlier than routine screening in women with risk factors for diabetes including prodiabetogenic medications such as glucocorticoids or calcineurin inhibitors. Managing anemia in pregnancy with concurrent CKD can be challenging due to increased iron requirements with dose increases of 30–50% required in pregnancy [106]. Erythropoietin (EPO)-stimulating agent dose may increase due to EPO resistance from increase cytokines production in pregnancy.

There are no data available on optimal timing of delivery in a CKD population and thus decisions should be based on local practice, and maternal and fetal health. Cesarean section is not specifically indicated other than for obstetric reasons, but rates are substantially higher in women with CKD or post transplant, likely due to need for emergency delivery [14, 45]. In patients with renal transplantation, cesarean sections should be performed with input from the transplant surgical team regarding anatomy. Breastfeeding while receiving medications considered safe in pregnancy should not be discouraged, as fetal drug exposure is minimal compared with intrauterine exposure and benefits may outweigh risks [107]. Contraceptive options should be discussed and implemented postpartum, and may require careful consideration based on patient preferences and guidelines for contraception in women with medical comorbidity [13].

Immunosuppression

Immunosuppression may require manipulation prior to conception for both transplanted women and those with glomerulonephritis [13], although the impact this has on renal outcomes is unknown. Observation for 3–6 months to ensure renal condition remains stable is recommended. Calcineurin inhibitors, glucocorticoids, and azathioprine are most commonly used and have no increased risk of

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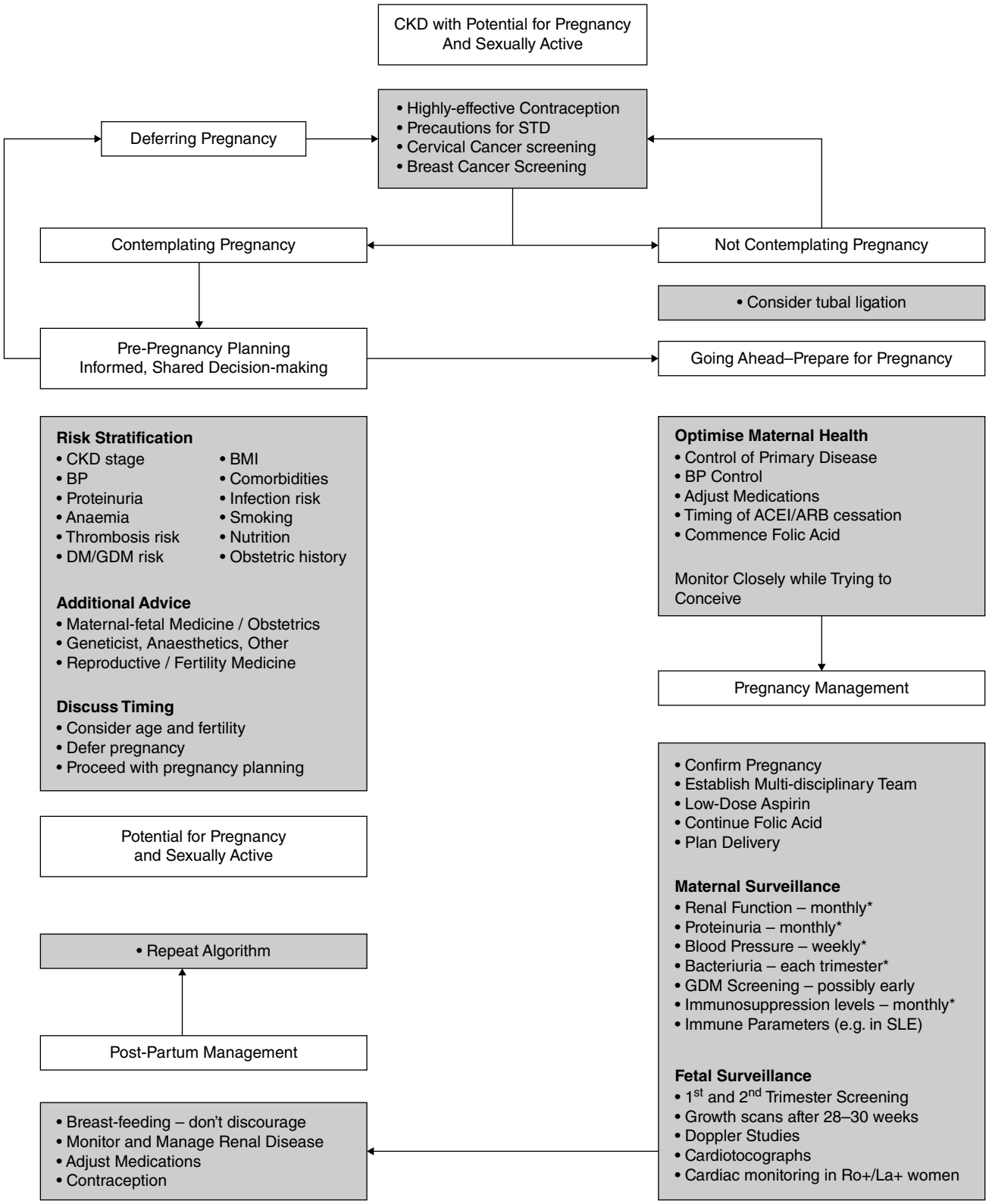

Figure 27.1 Algorithm for pregnancy management in women with CKD and transplant. *Or more frequently if required. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; CKD, chronic kidney disease; DM, diabetes mellitus; GDM, gestational diabetes mellitus; SLE, systemic lupus erythematosus; STD, sexually transmitted disease. *Source:* Adapted with permission from Fitzpatrick et al. [79]. © 2016, Dove Medical Press Limited.

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congenital malformation [51, 108–110]. Cyclosporine levels decline in pregnancy and require dose alteration [108]. Similarly, the pharmokinetics of tacrolimus are altered in pregnancy-related shifts in albumin and hematocrit, with a decrease in the inactive, bound fraction that is measured in assays. Tacrolimus trough levels reach a nadir in the second trimester [68, 108]. Subsequent dose alterations by up to 25% can increase the unbound active fraction that is not currently routinely measured, increasing toxicity risk [111, 112]. Mycophenolate mofetil causes birth defects and miscarriage [82, 83] so should be ceased 3 months prior to conception, usually with conversion to azathioprine, which is transferred to the fetus but not activated due to absence of inosinate pyrophosphorylase. Safety data on mammalian target of rapamycin in pregnancy is limited though it may affect fetal growth therefore cessation is advised [113]. Treatment of transplant rejection in pregnancy should be as per local practice. Options for treating acute glomerulonephritis, including SLE nephritis in pregnancy, are also limited, with reports of use of steroids, myophenolate mofetil cyclophosphamide, and rituximab, all of which have adverse safety profiles in pregnancy [13]. Tacrolimus may be a useful therapy for SLE nephritis in pregnancy but further data are required [114]. Women with SLE should receive hydroxychloroquine pre conception and throughout pregnancy due to fetal benefits [47].

Dialysis Management

There is no evidence base regarding when to initiate dialysis in pregnant patients with CKD [67]. Women with advanced CKD may require commencement of dialysis during pregnancy for maternal symptoms, hypertension or fluid management, or reducing urea levels, which improves fetal outcomes [115].

In women who conceive while receiving chronic hemodialysis, intensive dialysis has been demonstrated to improve fetal outcomes [3, 62] due to increased urea clearance causing less fetal solute diuresis and polyhydramnios [14]. Historically a target urea of under 17.9 mmol/l (50 mg/dl) was recommended [46], with further studies confirming better outcomes with low urea targets [3]. A large meta-analysis of 681 pregnancies from 126 studies reviewed dialysis schedule and pregnancy outcomes, demonstrating a relationship between greater number of dialysis hours and reduced risk of small gestational age and preterm delivery [3]. Intensive dialysis (>36 h/week) compared to <20 h/week was associated with higher live birth rates (85% vs. 48%), greater birth weight, and older gestational age [89]. Logistically, this is challenging but can be achieved through daily or nocturnal dialysis. The degree of residual renal function is important to outcomes [5, 64]. Less dialysis may be required if residual renal function is present, substantially reducing the dialysis burden [89].

Intensive dialysis offers better control maternal of hypertension and fluid status, although fetal and placental hypoperfusion from excessive fluid removal should be avoided, with regular clinical assessment as women gain weight [62, 89, 116]. Other sequelae of intense dialysis include electrolyte imbalance with risk of hypokalaemia, hypocalcaemia, and hypophosphatemia requiring dialysate changes [62, 116, 117]. Increased protein loss requires careful dietetic management of dietary protein intake [62, 118]. Increased folate supplementation to 5 mg/day is advised to reduce risk of neural tube defects [116].

There are few data on the use of peritoneal dialysis in pregnancy. Outcomes may be inferior to pregnancies managed with hemodialysis, but direct comparison cannot be made with the existing evidence base [3]. Increasing dialysis delivery through PD can be a successful management strategy, but a growing uterus may limit exchange volumes and clearance, and cause catheter migration [65].

Management of Transplanted Women

The management of women post kidney transplantation should incorporate the general principles as outlined above. Determining the appropriate timing of conception post transplant is a balance between stabilization of graft function and fitting into the window of fertility. Guidelines recommend conception only 1–2 years post transplantation [39, 119], although the optimal time is unknown and early pregnancy post transplant (within 3 years) may impact on graft function [74]. Registry data suggest most women wait 3–5 years before conceiving [66]. Prior to conception, graft function should be stable on pregnancy-safe immunosuppression, with controlled hypertension and low risk of rejection or infection [39, 119]. Other specific management includes adjustment of immunosuppression and other relevant medication such as antivirals and antihypertensives. Surveillance should be undertaken of allograft dysfunction, gestational diabetes, bacterial infection, particularly urinary tract, viral infection, including cytomegalovirus and herpes simplex virus, and vigilant monitoring for preeclampsia and rejection.

Conclusion

Many physiological changes occur during pregnancy affecting the kidney, and management of kidney disease in pregnancy presents a number of challenges to clinicians, particularly as the evidence base that underpins complex

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clinical decision-making is weak. Risk of adverse outcomes for mother and baby are present in even mild CKD and escalate with disease severity and added comorbidity. Experience in managing these complex pregnancies has increased over recent decades, with a change in approach to cautious optimism. The need to incorporate shared decision-making between patients, families, and a multidisciplinary team, with an understanding of patients' motivations and values, is an essential part of embarking on this journey with this group of high-risk women.

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28

ANCA-associated Vasculitis

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Introduction and Definitions

The antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAVs) are a group of systemic necrotizing vasculitides which affect small to medium-sized blood vessels. There is a spectrum of organ involvement, including the kidney, lungs, nerves, gut, and ear, nose, and throat (ENT). AAVs are classified on the basis of clinical and pathological features into granulomatosis with polyangitis (GPA), microscopic polyangitis (MPA), eosinophilc granulomatosis with polyangitis (EGPA), and renal limited vasculitis (RLV). The 2012 Chapel Hill Consensus Conference (CHCC) nomenclature of vasculitis defines AAVs as necrotising vasculitis which predominately affects small vessels such as capillaries, venules, arterioles, and small arteries. There must be few or no immune deposits present [5]. The CHCC definitions of GPA, MPA, and EGPA are summarized in Table 28.1. The CHCC is a nomenclature system rather than a diagnostic classification. The 1990 American College of Rheumatology (ACR) criteria provides diagnostic criteria for GPA and EGPA but not MPA; but ANCAs were not included as part of the diagnostic criteria. Based on the results of the Diagnostic and Classification Criteria for Vasculitis (DCVAS) study, new criteria for classification of GPA, EGPA, and MPA to standardize the classification of these diseases to support clinical research were co-jointly endorsed by the American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology (EULAR) have recently been published [6,7,8]. These classification criteria are shown in Table 28.2.

Prior to 1979 it was assumed that all cases of rapidly progressive glomerulonephritis (RPGN) were caused by immune complex deposition or circulating antiglomerular basement membrane (anti-GBM) antibodies. Stilmant et al. recognized that in fact many of these cases were pauci-immune, and in 1982 the first report of circulating ANCA associated with a pauci-immune glomerulonephritis (GN) was published [9, 10]. The two major targets of ANCA have been shown to be myeloperoxidase (MPO) and proteinase 3 (PR3), enzymes expressed in the granules and lysosomes of neutrophils and monocytes [11–13]. GPA is more commonly associated with PR3-ANCA positivity and MPA with MPO-ANCA, although there is considerable overlap and around 10% of patients with MPA or GPA will be ANCA negative. In EGPA around 40% of patients are reported to be ANCA positive, and vasculitic features such as GN are more

Table 28.1 Definitions for AAV.

Microscopic polyangiitis (MPA)	Necrotizing vasculitis, with few or no immune deposits, predominantly affecting small vessels. Necrotizing glomerulonephritis and pulmonary capillaritis are very common. No granulomatous inflammation is seen.
Granulomatosis with polyangiitis (Wegener's) (GPA)	Necrotizing granulomatous inflammation usually involving the upper and lower respiratory tract, and necrotizing vasculitis affecting predominantly small to medium vessels. Glomerulonephritis is common.
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss) (EGPA)	Eosinophillic necrotizing granulomatous inflammation, often involving the respiratory tract, and necrotizing vasculitis predominantly affecting small to medium vessels. Often associated with asthma and eosinophilia.

Source: Adapted from the Chapel Hill 2012 consensus on nomenclature of vasculitis [5].

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Table 28.2 ACR/EULAR Classification Criteria for ANCA-Associated Vasculitides (AAVs).

Granulomatosis with polyangiitis (GPA)		Microscopic polyangiitis (MPA)		Eosinophilic granulomatosis with polyangiitis (EGPA)	
Bloody nasal discharge, nasal crusting, or sino-nasal congestion	+3	Perinuclear ANCA or anti-myeloperoxidase ANCA positivity	+6	Maximum eosinophil Count >1 x 10^9/liter	+5
Cartilaginous involvement (Any of inflamed ear or nose cartilage, hoarse voice/stridor, endobronchial involvement or saddle nose)	+2	Pauci-immune glomerulonephritis	+3	Obstructive airway disease	+3
Conductive or sensorineural hearing loss	+1	Lung fibrosis or interstitial lung disease	+3	Nasal polyps	+3
Cytoplasmic antineutrophilic antibody (ANCA) or anti-proteinase 3 ANCA positivity	+5	Sino-nasal symptoms or signs	+3	Cytoplasmic ANCA or anti-proteinase 3 ANCA positivity	–3
Pulmonary nodules, mass, or cavitation of chest on imaging	+2	Cytoplasmic ANCA or anti-proteinase 3 ANCA positivity	–1	Mononeuritis multiplex/ motor neuropathy due to radiculopathy	+1
Granuloma or giant cells on biopsy	+2	Eosinophil Count >1 x 10^9/ liter	–4	Extravascular eosinophilic predominant inflammation	+2
Inflammation or consolidation of the nasal/ paranasal sinuses on imaging	+1			Hematuria	–1
Pauci-immune glomerulonephritis	+1				
Perinuclear ANCA or antimyeloperoxidase ANCA positivity	–1				
Eosinophil Count >1 x 10^9/liter	–4				
Total score of ≥5 for diagnosis of GPA		Total score of ≥5 for diagnosis of MPA		Total score of ≥6 for diagnosis of EGPA	
Sensitivity 93% (95%-CI 87-96%)		Sensitivity 91% (95%-CI 85-95%)		Sensitivity 85% (95%-CI 77-91%)	
Specificity 94% (95%-CI 89-97%)		Specificity 94% (95%-CI 92-96%)		Specificity 99% (95%-CI 98-100%)	

Adapted from reference 6-8.

common in the patients with ANCA positivity [14]. This chapter will focus on the management of MPA and GPA as there are several differences in the pathogenesis, features, and management of EGPA. A summary of the quality of the evidence and strength of the recommendation for treatment of the AAVs is shown in Table 28.3.

Epidemiology

AAVs are rare conditions with reported annual incidence between 13 and 20 cases per million individuals in Europe [15]. There is a slight male preponderance and peak age of onset of AAV has been reported as age 55–64, 65–74, and more than 75 years in different studies [16–18]. AAV is very rare in childhood. Within Europe there may be a geographical variation in AAV subtype, with reported higher incidence of GPA in Northern Europe and MPA in the south [19]. This trend to geographic variation was also present in studies conducted in the United States, where there is higher prevalence of GPA in northern states and more MPA in southern states. Studies comparing the UK and Japan showed a similar incidence of AAV in the two populations, but the majority of the Japanese population had MPA and GPA was extremely rare [20]. Within France, the prevalence of AAV was twice as high in those with a European background than in those of non-European ethnicity [21]. Studies in Sweden and the UK have both reported increasing incidence of AAV since the early 1980s although it is not clear whether this represents a true increase in disease or reflects greater awareness of the condition and the more widespread availability of ANCA testing [22, 23].

There is a genetic basis for AAV, and this may underlie some of the reported population differences. There are two published genome-wide association studies (GWAS), both carried out in patients of Northern European ancestry, which identified both MHC and non-MHC genetic associations with AAV [24, 25]. There is a stronger genetic association related to the antigenic specificity of ANCA than there is to clinical phenotype, and MPO-ANCA and PR3-ANCA may define differing diseases. In PR3-ANCA related disease there are strong associations with *PRTN3*, the gene which

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Table 28.3 Treatment for AAV.

Treatment	Recommendation	Certainty of evidence	Strength of recommendation
Remission induction			
Cyclophosphamide and corticosteroids	Oral or IV cyclophosphamide should be used for induction therapy in patients with severe or organ-threatening AAV. Pulsed treatment with IV cyclophosphamide is equivalent to oral treatment for remission induction but may result in increased risk of relapse.	High (IV vs. oral-low)	1A [1, 2]
Rituximab and corticosteroids	Rituximab is an alternative to cyclophosphamide, particularly in those who are unable or unwilling to receive cyclophosphamide such as patients wishing to preserve fertility. Some guidelines restrict the use of rituximab to those unable to receive cyclophosphamide. Rituximab may be superior to cyclophosphamide for remission induction in patients presenting with relapsing disease.	High	1B [1, 2]
Adjunctive plasma exchange in renal vasculitis	There is insufficient evidence for routine use of adjunctive plasma exchange but current guidelines recommend it for patients with RPGN, creatinine>500 μmol/l at diagnosis or those with pulmonary hemorrhage.	Low	2D [1, 2]
Remission maintenance			
Azathioprine	Azathioprine is as effective as oral cyclophosphamide for remission maintenance, but is safer with fewer adverse events.	Moderate	1B [1]
Rituximab	Rituximab is as effective as azathioprine in preventing major relapse with similar levels of adverse events. Some guidelines include rituximab as an alternative therapy for remission maintenance.	Moderate	1B [1]
MMF	MMF is less effective than azathioprine in preventing relapse but may be used as an alternative in patients who are intolerant or allergic to azathioprine. Guidelines vary as to whether MMF or methotrexate should be second line.	Moderate	1B [1]
Methotrexate	Methotrexate can be used for remission maintenance in patients unable to tolerate azathioprine. There are similar relapse rates in patients treated with methotrexate and those treated with azathioprine but more severe adverse events with methotrextate. Methotrexate should not be used in those with eGFR<30 ml/min and dose should be adjusted in patients with eGFR<60 ml/min. Guidelines vary as to whether MMF or methotrexate should be second line.	Moderate	1B/1C [1, 2]
Co-trimoxazole	There is no evidence to support the use of co-trimoxazole for remission maintenance.	Low	2B [2]

GRADE assessment of the evidence [3, 4]: High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different is low. Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different is moderate. Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different is high. Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different is very high.
AAVs, antineutrophil cytoplasmic antibody-associated vasculitides; eGFR (estimated GFR), ; IV, intravenous; MMF (Mycophenolate mofetil); RPGN, rapidly progressive glomerulonephritis.

encodes PR3, *SERPINA1*, the gene encoding α1-antitrypsin, and HLA-DP. MPO-ANCA-associated disease is linked to HLA-DQ polymorphisms. There are several other HLA and non-HLA genes which have been associated with AAV [26].

There are also several reported environmental associations with AAV such as toxins, drugs, and infections. In patients with ENT disease and anti-PR3 ANCA, infection may precede disease relapse and nasal carriage of *Staphylococci* correlates with relapse [27]. This may be due to molecular mimicry whereby antibodies against microbial antigens cross-react with self antigen [28]. Drugs, including propylthiouracil, hydralazine, and penicillamine, are associated with positive ANCA serology, and less commonly may be associated with clinical vasculitis [29, 30]. An association with levamisole-contaminated cocaine, positive ANCA serology, and clinical disease resembling GPA has also been

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reported [31]. Environmental triggers such as silica and heavy metal exposure have also been implicated as triggers. After the 1995 Kobe earthquake in Japan there was a regional threefold increase in disease incidence, suggesting that air pollutants can play a role in the etiology of disease [32]. In some studies, but not others, an association with farming has been reported [33, 34].

Pathogenesis

There are several clinical observations which support a role for ANCA being directly pathogenic. Most patients with AAV have circulating ANCA and in some studies ANCA titer has been shown to predict relapse [35]. There is a reported case of neonatal AAV following placental transfer of MPO-ANCA, resulting in renal disease and pulmonary hemorrhage shortly after birth [36]. Another case report describes no clinical disease despite maternal-fetal transfer of MPO-ANCA [37]. Removal of antibodies using plasmapheresis and use of B cell targeted therapies have both been shown to be effective treatments for AAV [38–40]. These findings are supported by experimental work from both in vitro experiments and in vivo models of AAV. Passive transfer models in mice, where anti-MPO antibodies are raised in MPO-deficient mice and then transferred into naïve recipients, results in the recipient mice developing a severe vasculitis with crescentic GN and pulmonary hemorrhage [41]. in vitro, neutrophils which have been primed with TNF(Tumor necrosis factor)α, lipopolysaccharide (LPS), or complement (C5a) can be activated by ANCA, causing degranulation, ROS production, and endothelial cell damage [42–44]. ANCA are also mediators of NETosis, a form of neutrophil cell death which occurs with release of neutrophil extracellular traps (NETs). Patients with AAV have increased levels of NETs in their circulation and NETs have been shown at sites of tissue damage in AAV [45]. Although there is much evidence for the pathogenicity of ANCA and ANCA-induced activation of neutrophils, ANCA are not always pathogenic. Ten percent of patients with AAV are ANCA negative, and ANCA can either persist in clinical remission or recur without evidence of relapse. Natural anti-MPO antibodies have been identified in healthy individuals and these are of lower avidity and titer than antibodies in patients with AAV [46]. One study of MPO-ANCA has shown that anti-MPO antibodies from healthy individuals had different target epitopes to anti-MPO antibodies from patients with AAV [47].

Complement is increasingly recognized to play a role in the pathogenesis of AAV. Mice deficient in C5 or depleted of complement did not develop disease in the passive antibody transfer model of AAV described above. C4-deficient mice were not protected, suggesting a role for the alternative and not the classical pathway [48]. Mice with knock-in of the human C5a receptor (C5aR) and MPO-AAV respond to treatment with an antagonist of human C5aR (CCX168; avacopan) and have decreased disease severity. A phase II trial has shown avacopan was noninferior to high-dose glucocorticoids when used in combination with rituximab or cyclophosphamide for induction of remission [49].

The mechanisms underlying the development of ANCA are less well understood. One suggested mechanism is that of molecular mimicry. An atypical ANCA, antihuman lysosome-associated membrane protein-2 (anti-LAMP-2) antibody, has been identified in patients with pauci-immune GN. It has 100% sequence homology with FimH, a protein present on gram negative bacteria, and when rats are immunized with FimH they develop GN and antibodies which cross-react with human and rat LAMP-2 [28]. Another potential mechanism is of anti-idiotype interactions to peptides complementary to the auto-antigen, such as complementary PR3 peptides which are homologous to some *Staphylococcus aureus* peptides [50]. There is also a role for disordered T cell responses: patients with AAV have defective Treg suppressor function and increased frequency of a T cell subset which is resistant to the suppressive effects of Tregs [51, 52]. Regulatory B cells have also been shown to be decreased in patients with AAV [53, 54].

Clinical Features

AAV is a multisystem disease and clinical presentation varies widely in both severity and organ involvement. Patients often have a nonspecific prodromal illness which may precede diagnosis by several weeks or months, with features such as fever, anorexia lethargy, arthralgia, or weight loss. Patients may have asymptomatic urinary abnormalities early in disease course (or in those with milder disease) but renal involvement typically presents as a RPGN. In MPA 90% of patients will have evidence of renal disease, compared to 80% of those with GPA and around 40% of those with EGPA [55]. In GPA extrarenal features of disease are common, with 90% of patients having lung or ENT involvement. Patients with MPA often have more severe renal involvement. Other organ systems involved include the skin, nervous system, eyes, musculoskeletal system, and gastrointestinal tract [55]. In EGPA patients typically have features of asthma and nasal polyps with peripheral blood eosinophilia. In patients with RPGN, as disease progresses, features of overt renal failure will develop and patients may have symptoms related to salt and water overload such as

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Table 28.4 Summary of diagnostic tests in patients with suspected AAV.

Investigation	Results/comments
FBC	Leucocytosis Thrombocytosis Normochromic normocytic anemia
CRP, ESR	Often raised but nonspecific
Renal function	Raised urea and creatinine in patients with RPGN
Complement C3, C4	Normal or elevated in AAV. Low C3/C4 may indicate bacterial infection such as endocarditis or immune complex GN. Isolated low C3 is seen in postinfectious GN or C3 glomerulopathy.
Immunoglobulins	Polyclonal hypergammaglobulinemia may be present. Prior to commencing cytotoxic therapies, hypogammaglobulinemia should be excluded.
Viral serology: HBsAg, HIV, HCV Ab	Prior to initiating immunosuppressive therapies
Blood cultures	To investigate for the presence of bacterial endocarditis in patients with ANCA positivity and systemic symptoms
ANCA	IIF or immunoassay
anti-GBM, ANA, dsDNA	To investigate for other causes of RPGN
Urine dipstick	Hematuria and proteinuria. Leukocyturia often represents the presence of nonspecific inflammatory cells.
Urine microscopy	Needs to be performed by a skilled operator on fresh urine. Red cell casts are seen in glomerulonephritis.
Urine PCR	Low-grade proteinuria is common. In RPGN decreased glomerular blood flow limits protein filtration.
Renal biopsy	Pauci-immune, necrotizing, creacsentic GN
Skin biopsy	Leukocytoclastic vasculitis
ENT or lung biopsy	Granuloma often seen
Nerve biopsy	Necrotizing vasculitis of associated small and medium blood vessels
Pulmonary function testing	Raised KCO in 25% of patients with pulmonary hemorrhage

AAV, ANCA-associated vasculitis; ANA, anti-nuclear antibody; ANCA, Anti-neutrophil cytoplasmic antibody; anti-GBM, anti-glomerular basement antibody; C3, complement component 3; C4, complement component 4; CRP, C-Reactive Protein; dsDNA, double stranded DNA; ENT, Ear-Nose-Throat; ESR, Erythrocyte Sedimentation Ratio; FBC, Full blood count; GN, Glomerulonephritis; HBsAg, Hepatitis B surface antigen ; HCV Ab, Hepatitis C Virus antibody; HIV, Human immunodeficiency virus; IIF, indirect immunofluorescence; RPGN, rapidly progressive glomerulonephritis.

breathlessness, cough, orthopnea, and peripheral oedema or to uremia such as itch, anorexia, and fatigue. Relapse of disease is common and occurs in 30–50% of patients.

Diagnostic Tests

The usual screening test for ANCA is to perform indirect immunofluorescence (IIF) on neutrophils; positive samples are then used in antigen-specific immunoassays to determine ANCA specificity. Due to the increasing availability of high-quality immunoassays for MPO- and PR3-ANCA, the current consensus is that these tests can be used for screening without absolute need for IIF [56]. In patients with renal involvement a renal biopsy is usually performed. The diagnostic tests used to diagnose and evaluate AAV are summarized below and in Table 28.4.

Hematological and Biochemical Tests

Full blood count may show leucocytosis, thrombocytosis, or normochromic normocytic anemia. Raised C reactive protein and erythrocyte sedimentation rate are often present. Raised urea and creatinine will be present in those with RPGN. Urine dipstick may show hematuria, proteinuria or leukocyturia, and urine microscopy should be used to confirm the presence of hematuria and to identify red cell casts. Urinary protein leak should be quantified using a spot urine protein:creatinine ratio (uPCR); proteinuria is

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often low grade (<100 mg/mmol) and usually will be subnephrotic (<300 mg/mmol) [57].

Imaging

Chest imaging (radiograph or computed tomography) should be undertaken in all patients with respiratory symptoms such as cough, dyspnea, or hemoptysis, and may show pulmonary infiltrates suggestive of hemorrhage, nodules or cavitation. There should be a low threshold for chest screening in patients in whom a diagnosis of AAV is suspected.

Renal imaging with ultrasound should be performed to exclude structural kidney diseases prior to renal biopsy, but in patients with AAV will usually be normal or show nonspecific features of acute kidney disease such as changes in echogenicity. Other imaging should be directed toward symptoms such as imaging of the sinuses, gut, retro-orbital space or nervous system.

Physiological Testing

Lung function testing may show an increased diffusing capacity for CO (KCO) in pulmonary hemorrhage, whereas it should be low in other causes of pulmonary infiltrates such as pulmonary oedema. However, raised KCO is only present in 25% of patients with pulmonary hemorrhage and normal or low KCO does not have a good negative predictive value [58]. Patients with pulmonary hemorrhage may also be too unwell to undergo testing. Other physiological tests will be guided by the patient's clinical presentation, such as nerve conduction studies or echocardiography.

ANCA Testing

Indirect Immunofluorescence

IIF is usually performed on ethanol-fixed neutrophils, with two patterns of staining seen in positive samples: cytoplasmic (c-ANCA), which is associated with anti-PR3 antibodies, and perinuclear (p-ANCA), which is typically seen with anti-MPO antibodies. An atypical pattern is seen rarely and comprises cytoplasmic, perinuclear, and nuclear staining; it is associated with several antigen specificities [59]. The perinuclear pattern seen with MPO-ANCA arises due to the process of ethanol fixation, which leads to MPO dissolving from the neutrophil granules and attaching to the nucleus. When formalin-fixed neutrophils are used this does not occur and a cytoplasmic pattern is seen with both MPO and PR3-ANCA. Atypical ANCA IIF can be seen in other diseases such as inflammatory bowel disease, HIV, bacterial endocarditis, or related to drug-induced autoimmunity. A range of atypical target antigens have been described, including lactoferrin or elastase.

Antigen Specific Tests

Several immunoassays are available, including enzyme immune-assays (EIAs), bead-based multiplex assays, fluorescent enzyme immune assays (FEIA), and immunoblot assays. These assays usually detect IgG and provide quantitative results. It was previously recommended that a positive IIF should be followed by an antigen-specific test, however recent studies have shown that immunoassays are more sensitive and specific than IIF [60]. Additionally, IIF can be labor intensive and automated interpretation is not available worldwide. Current guidelines recommend immunoassay testing for PR3 and MPO-ANCA for diagnosis of AAV without need for IIF [56]. In patients with a high index of suspicion for AAV, IIF should be carried out despite negative immunoassay results. Anti-MPO or anti-PR3 antibodies have good positive predictive values for the diagnosis of AAV but have been reported in other inflammatory conditions and are not diagnostic. A histological diagnosis is required for definitive diagnosis where possible [61].

Histological Tests

In patients with clinical evidence of renal disease such as urinary abnormalities or deranged renal function, renal biopsy is the gold standard for diagnosis. The typical pattern of glomerular injury seen on light microscopy is of necrotizing and crescentic GN: immunofluorescence will show minimal or negative staining for immunoglobulin or complement, and electron microscopy may show microthrombi or degranulation of neutrophils but no or minimal immune deposits [62, 63]. A histopathological classification system has been developed for AAV with four categories of disease: focal, where <50% of glomeruli are affected, crescentic, where >50% of glomeruli contain cellular crescents, sclerotic, where >50% of glomeruli are globally sclerosed, and mixed, where normal, crescentic, and sclerotic glomeruli are all present and >50% of glomeruli are affected [63]. The classification system has been shown to predict renal outcomes in AAV with patients with sclerotic lesions least likely to recover renal function. [63] Biopsy of other sites of disease may also be undertaken, such as skin, ENT, lung, or nerve, particularly if there is diagnostic uncertainty.

Treatment

Modern immunosuppression regimes have transformed patient outcomes in patients with AAV. Prior to the 1960s, mortality at 1 year was as high as 80%, whereas current studies show 1 year survival of around 90% [64]. Usually an initial period of intense immunosuppression is used to

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induce remission followed by a period of sustained low-dose treatment to prevent relapse.

Remission Induction

The most widely used first-line treatment regimen for induction of remission in patients with AAV and severe disease is cyclophosphamide Table 28.1 and high-dose glucocorticoids with the addition of plasma exchange for those with severe renal impairment or RPGN. An example induction treatment regimen is shown in Table 28.5.

Cyclophosphamide

Several clinical trials have studied the optimum route, dose, and duration of treatment with cyclophosphamide. There are four published studies of oral versus pulsed intravenous (IV) cyclophosphamide, the largest and most recent of which is the Randomized Trial of Daily Oral vs Pulse Cyclophosphamide as Therapy for ANCA-Associated Systemic Vasculitis (CYCLOPS) trial, which included 149 newly diagnosed patients with either GPA or MPA and renal involvement, but not life-threatening disease Table 28.7 [65]. It showed no difference in time to remission between the two groups, but lower cumulative cyclophosphamide doses in the IV arm with lower rates of leukopenia [65]. Long-term follow-up of this study showed higher relapse rates in the group treated with IV cyclophosphamide but no difference in ESRD, morbidity, or mortality [66]. Of the available published guidelines, European League Against Rheumatism (EULAR)/European Renal Association – European Dialysis and Transplant Association (ERA-EDTA) and British Society of Rheumatology (BSR) guidelines favor IV over oral cyclophosphamide, and Kidney Disease Improving Global Outcomes (KDIGO) recommend either oral or pulsed IV cyclophosphamide at clinician discretion [1, 2, 67] Table 28.6. Only one study has investigated the duration of treatment with IV cyclophosphamide (without subsequent maintenance therapy) and it showed no difference in mortality, duration of remission, or infection rate between six and 12

Table 28.5 Initial treatment of severe AAV [1, 2].

Agent	Route	Initial dose	Comments
Cyclophosphamide	IV, oral	IV: 15 mg/kg every 2 weeks for three pulses then every 3 weeks PO: 1.5–2 mg/kg/day	Reduce dose in severe renal impairment or in older patients (>60 years)
Glucocorticoids	IV, oral	IV methylprednisolone for 3 days PO prednisolone 1 mg/kg/day (max. 60 mg) for 4 weeks then gradual taper 3–4 months	
Rituximab	IV	375 mg/m^2 weekly for 4 weeks or 2 × 1 g infusions 2 weeks apart	Alternative to cyclophosphamide in some guidelines [1]
Plasma exchange		60 ml/kg volume replacement to a maximum of 4 l with human albumin solution or fresh frozen plasma if bleeding risk (pulmonary hemorrhage or recent kidney biopsy)	Monitor platelet count (aim >70 × 10^9/l); fibrinogen (aim >1 g/l and replace with cryoprecipitate if necessary); corrected calcium (aim normal range)

IV, intravenous; PO (Per os)

Table 28.6 Summary of evidence for pulsed vs. oral cyclophosphamide induction therapy for AAV.

Outcome	Number of participants (number of studies)	Comparative risks		Relative effect	Quality of evidence (GRADE)
		Continuous CYC	Pulsed CYC		
Death	278 (4)	206/1000	159/1000 (91–272)	RR 0.77 (0.44–1.32)	Low
RRT	245 (4)	74/1000	141/1000 (68–289)	RR 1.9 (0.92–3.91)	Low
Relapse	235 (4)	181/1000	324/1000 (201–519)	RR 1.79 (1.11–2.87)	Low
Serious infections	278 (4)	348/1000	247/1000 (132–463)	RR 0.71 (0.38–1.33)	Very low

AAV, antineutrophil cytoplasmic antibody-associated vasculitides; CYC, cyclophosphamide; RR, ;RRT, renal replacement therapy.
Source: Data drawn from Cochrane review of the evidence [3].

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Table 28.7 Summary of clinical trials investigating pulsed vs. oral cyclophosphamide induction therapy for AAV.

Study	Design	Primary end point	Results	Secondary end points	Comments
CYCLOPS [65]	Open label, parallel RCT Daily oral vs. pulsed CYC	Time to remission	No difference: median 3 months in both groups No difference in proportion in remission	Lower cumulative CYC does in pulsed IV group and lower incidence of leukopenia No difference in other adverse events or death	Lower relapse rates in daily oral CYC group on retrospective long-term follow-up (median 4.3 years) Low risk of bias
Adu 1997 [70]	Parallel RCT Daily oral CYC followed by AZA (at median 3 months) vs. pulsed CYC	Drug toxicity	More leukopenia in CCAZP group	No difference in number in complete remission at final follow-up, relapse rates, death or requirement for RRT	Patients in pulsed group had poorer renal function at baseline than oral group
Guillevin 1997 [71]	Parallel RCT Daily oral vs. pulsed CYC	Remission induction and death	No difference in proportion of patients in remission at 6 months No difference in 5-year survival	Greater relapse rates in pulsed CYC group Lower cumulative CYC dose in pulsed group and fewer severe side effects (infection, PCP)	Recruitment terminated early due to significantly differing rates of severe side effects and relapse rates between the groups
Haubitz 1998 [72]	Parallel RCT Daily oral vs. pulsed CYC	Disease progression Nonremission at 12 months Relapse up to 1 year after end of CYC Severe adverse events	Patient survival, remission rate, relapse rate similar between two groups Decreased cumulative CYC dose, and leukopenia and severe infections in IV group		Four patients excluded due to protocol violations Study terminated early when significant differences between the two groups found

AAV(ANCA-associated vasculitis), AZA, azathioprine; CCAZP(oral cyclophosphamide followed by azothioprine); CYC, cyclophosphamide; PCP, *Pneumocystis jirovecci* pneumonia; RCT(Randomized control led trial).

pulses. There were fewer relapses in the group of patients treated with 12 pulses [68]. Published guidelines recommend 3–6 months treatment with oral cyclophosphamide based on time to remission in studies of maintenance therapy [69].

Glucocorticoids

High-dose glucocorticoids should be used as part of initial treatment, but there is limited evidence for the benefit of IV pulsed methylprednisolone other than in the MEPEX trial, where it was shown to be less efficacious than plasma exchange (PEX) when added to cyclophosphamide and oral steroids for severe disease [38]. Dose and duration of oral steroids varies between published guidelines, and duration of therapy is often guided by patient response and relapse. There are no published studies comparing glucocorticoid regimens; one meta-analysis of 13 studies concluded that studies with longer courses of glucocorticoids were associated with fewer relapses although there was considerable heterogeneity between other immunosuppressive agents used between studies [73]. The Plasma Exchange and Glucocorticoids in Severe ANCA- Associated Vasculitis (PEXIVAS) trial is a large multicenter RCT including patients with moderate to severe renal impairment (eGFR(estimated GFR)<50 ml/min) or pulmonary hemorrhage, which was designed to provide definitive answers regarding PEX in AAV but also included a comparison of high- and low-dose glucocorticoid in both arms [74]. It showed that a reduced dose of oral glucocorticoid (following pulsed IV methylprednisolone in both groups) was noninferior on the composite primary end point of ESRD or death and was associated with fewer serious infections [75].

Plasma Exchange

Current guidelines advocate the addition of PEX as adjunctive therapy in patients with severe pulmonary or renal disease, particularly those who are refractory to initial treatment with cyclophosphamide and high-dose glucocorticoids. The largest published study to date, MEPEX, included 137 patients with severe renal disease (creatinine >500 μmol/l or dialysis requiring at presentation) and randomized them to either receive seven plasma exchanges or IV methylprednisolone. There was improved renal survival in the PEX group

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at 3 months and decreased requirement for dialysis at 12 months [38]. Long-term follow-up of this group (median follow-up of 3.95 years) showed no difference in a primary composite end point of death or ESRD [76]. There are seven other published studies investigating plasma exchange as an adjunctive therapy. A Cochrane review and a meta-analysis have both reviewed the current evidence for PEX in AAV (summarized in Table 28.8) [3, 77]. Both concluded that PEX may be of benefit in preventing ESRD and death at 1 year, however this was not thought to be conclusive as the overall quality of the evidence is low and there is heterogeneity between included studies [77]. The PEXIVAS trial (described above) has been reported in abstract form and has shown no benefit of PEX on the primary composite outcome of death from any cause or ESRD (28% of PEX group vs. 31% in the no-PEX group, HR 0.86, 95% CI 0.65–1.13, $P = 0.27$). Further subgroup analysis and publication of the full trial is awaited [75].

Rituximab

Rituximab is recommended in most guidelines as an alternative induction agent in patients who are unable to receive or who are resistant to cyclophosphamide; the EULAR/ERA-EDTA guidelines recommend treatment with either agent with no requirement for intolerance or resistance to cyclophosphamide [1, 2].

There are two published RCTs comparing rituximab to cyclophosphamide in AAV for first-line induction therapy [39, 78]. Both studies used a dose of rituximab of 375 mg/m^2 body area weekly for 4 weeks, and patients received high-dose glucocorticoids initially. In the rituximab versus cyclophosphamide in ANCA-associated renal vasculitis (RITUXIVAS) trial, patients in the rituximab arm also received two doses of IV cyclophosphamide with the aim of ensuring early control of severe disease [39]. Rituximab was noninferior to cyclophosphamide in both trials, and in the Rituximab for the Treatment of Wegener's Granulomatosis and Microscopic Polyangiitis (RAVE) trial, rituximab seemed to be more effective than cyclophosphamide for those with disease relapse rather than de novo presentation. Subgroup analysis of patient in the RAVE trial who had evidence of renal impairment showed that rituximab was also noninferior to cyclophosphamide in these patients, although the trial did not include a large number of patients with severe renal involvement (median eGFR at trial entry was 41 ml/min in the rituximab group and 50 ml/min in the cyclophosphamide group) [79]. These trials and a summary of the evidence for rituximab induction therapy are shown in Table 28.9 and Table 28.10. Remission induction using a combination of low-dose cyclophosphamide and rituximab in combination with a steroid-sparing approach has been described in an open-label cohort study. Long-term outcomes in this

Table 28.8 Summary of evidence for adjunctive PEX in AAV.

Outcome	Number of participants (number of studies)	Comparative risks		Relative effect	Quality of evidence (GRADE)
		Control	Plasma exchange		
Death at 1 year	267 (5)	189/1000	195/1000 (117–310)	RR 1.03 (0.62–1.64)	Low
Dialysis at 1 year	235 (6)	376/1000	169/1000 (109–271)	RR 0.45 (0.29–0.72)	Low
Serious infections	252 (4)	220/1000	262/1000 (167–405)	RR 1.19 (0.76–1.84)	Low

AAV,(ANCA-Associated Vasculitis); PEX,(Plasma Exchange); RR(relative risk),
The authors of the Cochrane review comment on the heterogeneity of the available studies with some being of high quality but others with significant problems and risk of bias.
Source: Data drawn from Cochrane review of the evidence [3, 77].

Table 28.9 Summary of evidence for rituximab as induction therapy in AAV.

Outcome	Number of participants (number of studies)	Comparative risks		Relative effect	Quality of evidence (GRADE)
		CYC	RTX		
Remission at 6 months	236 (2)	661/1000	720/1000 (608–853)	RR 1.09 (0.92–1.29)	Moderate
Serious infections	241 (2)	92/1000	84/1000 (39–180)	RR 0.91 (0.42–1.96)	High

AAV,(ANCA-Associated Vasculitis); CYC, cyclophosphamide; RR(relative risk); RTX, rituximab.
Source: Data drawn from Cochrane review of the evidence [3].

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Table 28.10 Summary of clinical trials investigating rituximab vs. cyclophosphamide as induction therapy for AAV.

Study	Design	Primary end point	Results	Secondary end points	Comments
RITUXIVAS [37]	Parallel RCT Rituximab vs. CYC in a 3 : 1 ratio	Sustained remission at 12 months Severe adverse events	No difference in remission rates at 12 months (76% RTX vs. 82% CYC) No difference in rates of severe adverse events	No difference in mortality	Patients in the RTX arm also received two pulses of IV CYC with doses 1 and 3 of RTX
RAVE [76]	Parallel RCT	Complete remission without prednisolone during the first 6 months	No difference in remission rates (64% in RTX arm, 53% in CYC arm)	No difference in adverse events	Rituximab superior in those with relapsing disease

AAV(ANCA-Associated Vasculitis); CYC, cyclophosphamide; IV, intravenous; RCT(Randomized control led trial); RTX, rituximab.

group were favorable when compared to historical cohorts and a prospective trial of this treatment regimen may be warranted [80].

Other Induction Agents

Several studies have compared other induction agents to cyclophosphamide in AAV and these could be considered for resistant disease but are not currently recommended for severe disease in published guidelines.

There are three trials which have compared MMF(Mycophenolate mofetil) to cyclophosphamide for induction of remission. The Mycophenolate Mofetil versus Cyclophosphamide for Remission Induction of ANCA-Associated Vasculitis (MYCYC) trial was a noninferiority trial comparing 6 months of induction with MMF to 6–10 pulses of IV cyclophosphamide, which to date has only been presented in abstract form, and it failed to demonstrate noninferiority of MMF [81]. Cochrane review of the three trials showed remission at 6 months was better with MMF compared to cyclophosphamide (RR(relative risk ratio) 1.17, CI 1.02–1.35), and there were no difference in adverse event rates between the groups [3, 81–83]. Patients with RPGN or severe renal failure were excluded from these studies.

One trial has compared methotrexate to cyclophosphamide, showing it to be noninferior with no difference in mortality or rates of remission at 6 months. Again, patients with severe renal impairment were not included in this trial and there was longer time to remission and higher relapse rates at 18 months in patients treated with methotrexate. Median time to relapse was 13 months in those treated with methotrexate and 15 months in the cyclophosphamide group [84, 85].

Based on the studies using MMF and methotrexate published guidelines recommend the use of either of these agents in patients with mild and nonorgan-threatening disease, with a preference for MMF in those who have evidence of renal involvement.

Other studies have investigated intravenous immunoglobulin, infliximab, and alemtuzumab and these could be considered for resistant disease [86–89].

Remission Maintenance

Current guidelines recommend that patients with severe AAV who are in remission after induction therapy with high-dose glucocorticoids plus cyclophosphamide/rituximab should be treated with low-dose glucocorticoids plus another immunosuppressive agent. Most commonly, azathioprine is recommended with methotrexate or MMF as an alternative [2, 69]. Introduction of azathioprine at 6 months after induction therapy has been shown to be noninferior to continuing cyclophosphamide to 12 months on rates of relapse at 18 months, and is associated with fewer adverse events [90]. Long-term follow-up of this study suggested there may be greater frequency of relapse in the group treated with azathioprine although this was not statistically significant [91]. Azathioprine has also been shown to be superior to MMF for remission maintenance but with similar rates of adverse events in MMF and azathioprine groups [92]. One trial has shown similar rates of relapse in patients treated with methotrexate or azathioprine for remission maintenance; however, the primary end point of this trial was safety of methotrexate rather than efficacy [93]. There were similar numbers of adverse events between the two groups but severity of adverse events was greater in those treated with methotrexate [93]. These studies are summarized in Table 28.11.

One RCT has investigated the duration of azathioprine maintenance therapy comparing tapering after 1 year or 4 years in patients with anti-PR3 AAV. This showed no significant difference in relapse-free survival at 4 years

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Table 28.11 Summary of evidence for azathioprine maintenance therapy in AAV.

Study	Design	Number of participants	Primary end point	Results	Secondary end points	Outcomes	Comparative risks		Relative effect	Quality of evidence (GRADE)
							Comparator	AZA		
CYCAZAREM [90]	Parallel RCT AZA vs. oral CYC following CYC/steroid induction	144	Relapse rate at 18 months	No difference in relapse rate (15.5% AZA, 13.7% CYC)	No difference in mortality or adverse events	Relapse	137/1000	155/1000 (70–342)	RR 1.13 (0.51–2.50)	Moderate
						Infections	178/1000	183/1000 (91–361)	RR 1.03 (0.51–2.03)	Moderate
WEGENT [93]	Parallel RCT AZA vs. MTX after pulsed CYC/steroid induction	126	Adverse reaction causing death or withdrawal of study drug	No difference (11.1% AZA, 19% MTX)	No significant difference in relapse rate	Adverse event	190/1000	110/1000 (48–262)	RR 0.58 (0.25–1.38)	Moderate
						Relapse	333/1000	366/1000 (226–589)	RR 1.1 (0.68–1.77)	Moderate
IMPROVE [92]	Parallel open-label RCT AZA vs. MMF after CYC/steroid induction	156	Relapse-free survival	More relapses in MMF group (55% vs. 37.5% in AZA group)	No difference in adverse events	Relapse	552/1000	375/1000 (265–531)	RR 1.47 (1.04–2.09)	Moderate

AAV(ANCA-Associated Vasculitis); AZA; azathioprine; CYC, cyclophosphamide; MMF(Mycophenolate mofetil); MTX; methotrexate; RCT(Randomized control led trial); RR(relative risk ratio); RTX, rituximab.
Source: Data drawn from Cochrane review of the evidence [3].

Table 28.12 Summary of evidence for rituximab maintenance therapy in AAV.

Study	Design	Number of participants	Outcome	Comparative risks		Relative effect
				AZA	RTX	
MAINRITSAN [40]	Parallel RCT RTX or AZA after CYC/steroid induction	118	Major relapse within 28 months	293/1000	52/1000 (18–170)	RR 0.17 (0.06–0.58)
			Severe adverse events	138/1000	193/1000 (42–228)	RR 0.71 (0.31–1.65)
				Fixed	Tailored	
MAINRITSAN 2(98)	RCT Tailored or fixed schedule rituximab	162	Relapse within 28 months	99/1000	173/1000 (77–389)	RR 1.75 (0.78–3.94)

AZA, azathioprine; CYC, cyclophosphamide; RCT(Randomized control led trial); RR(relative risk ratio); RTX, rituximab.

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between the two groups [94]. The prolonged Remission-Maintenance Therapy in Systemic Vasculitis (REMAIN) study also investigated duration of maintenance therapy and included 117 patients with stable remission following induction with cyclophosphamide and prednisolone. It showed that more prolonged maintenance treatment with azathioprine and prednisolone (48 months vs. 24 months) was associated with significantly lower risk of relapse. The prolonged treatment group had better renal outcomes but there was no difference in patient survival [95].

Rituximab is increasingly being used as an agent for remission maintenance in some centers. The Maintenance of Remission using Rituximab in Systemic ANCA-associated Vasculitis (MAINRITSAN) trial included 115 patients who were randomized to either rituximab or azathioprine for remission maintenance after induction therapy with cyclophosphamide and glucocorticoids Table 28.12 [40]. Rituximab was superior to azathioprine in preventing relapses (5% vs. 29% at 28 months) and adverse event rates were similar between the two groups. Long-term follow-up of this study shows that rituximab remains superior at 60 months (relapse free survival 37.2% vs. 57.9%). Again, the adverse event profile was similar between the two groups [96]. The MAINRITSAN 2 trial went on to compare fixed rituximab dosing every 6 months to a patient-tailored approach with rituximab re-dosing when CD19+ B cells or ANCA returned. Relapse rates were similar between the two arms (17.3% relapse rate in the tailored group vs. 9.9% in the scheduled treatment group); the tailored treatment group received fewer rituximab infusions over the study period [97].

Treatment of Relapse

Relapse is usually treated in the same way as patients presenting with de novo disease. Patients with minor relapses may respond to an increase or reintroduction of their oral immunosuppression or steroids. Those with severe relapse should be treated with high-dose glucocorticoids with cyclophosphamide or rituximab. Long-term follow-up of the RAVE study suggested that relapsing patients may respond better to rituximab than cyclophosphamide [79]. Additionally, cumulative cyclophosphamide exposure should be taken into account when planning to re-dose patients.

Co-trimoxazole

Prophylaxis against *pneumocystis jirovecci* is recommended in all patients receiving induction therapy with cyclophosphamide or rituximab. First-line treatment is with co-trimoxazole with pentamidine nebulizers as second line. There are also two studies which have investigated the role of co-trimoxazole in relapse prevention in patients with PR3-ANCA disease [98, 99]. There was a suggestion that the use of co-trimoxazole may reduce the risk of relapse at 1 year, particularly pulmonary relapse, but Cochrane review of the two studies found this result to be nonstatistically significant and so a firm conclusion regarding the use of antibiotics for remission maintenance was not possible (Table 28.13) [3].

Prognosis

Current studies estimate survival in patients with AAV to be around 90% at 1 year and around 70% at 5 years, a significant improvement following the introduction of modern immunosuppression regimens [64, 100]. A substantial cause of mortality within the first year is infection rather than active vasculitis, emphasizing the need for further research into better targeted therapies with better side-effect profiles [101, 102]. One year survival free of ESRD is approximately 75% and is 50% at 5 years [64]. The increased mortality in patients with AAV persists at long-term follow-up with increased rates of thrombosis, cardiovascular disease, malignancy, and infections when compared to the general population [102, 103]. In one study, predictors of mortality included advanced renal failure and older age [101]. Despite this, it is not the case that older patients should not be considered for aggressive treatment. One multicenter retrospective analysis of patients ≥75 years showed that patients who were not treated with cyclophosphamide or rituximab had significantly lower survival at 2 years (72.9% with cyclophosphamide, 81.3% with rituximab, and 45.0% with no/other treatments) [104].

Despite the improvements in mortality, in patients who have renal disease as part of their AAV the risk of relapse has remained relatively constant over recent years. One large

Table 28.13 Summary of evidence for antibiotics as maintenance therapy in AAV.

Outcome	Number of participants (number of studies)	Comparative risks		Relative effect	Quality of evidence (GRADE)
		Placebo	Co-trimoxazole		
Remission at 1 year	111 (2)	796/1000	907/1000 (780–1000)	1.14 (0.98–1.33)	Low

The authors comment that one of the two studies has multiple limitations in the study design.
Source: Data drawn from Cochrane review of the evidence [3].

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study has shown a cumulative relapse rate of 11% at 1 year and 35% at 5 years with no change in relapse rates over the 25 year study period [64]. Patients with PR3-ANCA disease are more likely to experience relapse than those who are MPO-ANCA positive or ANCA negative; presence of lung disease and older patient age have also been shown to predict relapse in some studies [105, 106]. The utility of ANCA titer for predicting relapse is debatable although it may correlate better in patients with renal disease where some studies have shown rising ANCA titer may predict relapse [35, 107].

Patients with AAV who require renal transplant have clinical outcomes which are comparable or better to those with other causes of ESRD [108]. Transplant should be deferred until patients are ≥1 year from remission as one study has shown that risk of death post transplant was greatest in those transplanted less than a year after remission [109]. The risk of recurrent disease is low after transplantation and relapse rates seem to be lower in more modern studies, possibly due to the current transplant immunosuppression regimens used [108, 110].

Conclusions

AAV are a group of rare, multisystem, small and medium vessel vasculitides. Modern immunosuppression regimens using more effective and targeted drugs have significantly improved morbidity and mortality, and mortality in the first year is more likely to be due to complications of treatment than active vasculitis. There are several available evidence-based guidelines for treatment which are based on high-quality RCTs. Most authorities recommend induction treatment with high-dose glucocorticoids plus cyclophosphamide or rituximab and maintenance therapy with low-dose glucocorticoids and azathioprine.

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Paraprotein-associated Kidney Disorders

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Introduction

Monoclonal gammopathies consist of a heterogenous group of disorders defined by the presence in serum and/or urine of a paraprotein produced by an abnormal B-cell clone. The clone usually derives from plasma cells when the paraprotein is IgG, IgA, IgD, or light chain only and $CD20^+$ lymphocytic clones including lymphoplasmacytic clones when it involves an IgM. In its advanced state, monoclonal gammopathy may indicate symptomatic malignant disorder such as multiple myeloma, Waldenström macroglobulinemia, or other non-Hodgkin lymphomas. More frequently, the clone can remain quiescent for a prolonged period of time defining monoclonal gammopathy of undetermined significance (MGUS) [1].

Renal complications associated with monoclonal gammopathy are frequent. They can be separated into two categories according to the characteristics of the underlying B-cell clone. The first group of renal diseases always occurs in the setting of high tumor mass with production of large amounts of monoclonal immunoglobulins. The prime example is light-chain cast nephropathy, which almost invariably complicates high tumor mass B-cell disorder, particularly symptomatic multiple myeloma [2–4]. Although rare, another example is glomerular deposition of monoclonal IgM during high tumor mass lymphoplasmacytic lymphoma (Waldenström macroglobulinemia) [5]. The second group includes all renal disorders caused by a monoclonal immunoglobulin secreted by a nonmalignant B-cell clonal disorder that does not require treatment for the tumor burden. These are currently referred to as monoclonal gammopathy of renal significance (MGRS) [6, 7]. In this setting, structural peculiarities of the paraprotein, particularly the variable domain, and not the rate of production are the main determinants of renal lesions [6, 8]. The spectrum of renal diseases in MGRS is vast and can be classified according to the localization of renal lesions (glomerular, tubular, vascular, etc.), and to the composition and the pattern of ultrastructural organization of deposits. Tubular lesions include light-chain proximal tubulopathy related to endolysosomal engorgement of proximal tubular cells by light chains and crystal-storing histiocytosis defined by crystalline inclusions within interstitial histiocytes. Glomerulopathies are featured either by organized deposits which can be fibrillar (Ig-related amyloidosis), microtubular (type I and type II cryoglobulinemic glomerulonephritis, immunotactoid glomerulopathy), or crystalline deposits (crystalglobulinemic glomerulonephritis), or by nonorganized deposits (monoclonal immunoglobulin deposition disease [MIDD] and proliferative glomerulonephritis with monoclonal immunoglobulin deposits [PGNMID]). The third subgroup includes glomerular lesions not induced by the deposition of the monoclonal immunoglobulin but by its functional activity. The most common is C3 glomerulopathy associated with monoclonal gammopathy where deposits are composed of C3 complement fraction only, consecutive to local or systemic activation of the complement alternative pathway (CAP) by the monoclonal immunoglobulin [9, 10].

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Diagnostic Evaluation

The diagnosis of monoclonal immunoglobulin-related kidney diseases almost always requires a kidney biopsy. The only exception is Ig-related amyloidosis, where the diagnosis could be made from other tissue [11]. Renal pathological diagnosis relies on careful examination of kidney biopsy samples by light microscopy, immunofluorescence studies, and electron microscopy [9, 12]. At a minimum, immunofluorescence studies must include antibodies against kappa and lambda light chains to determine monoclonality. Determination of IgG subclasses would help support the monoclonal nature of the immunoglobulin deposits, especially if a monoclonal immunoglobulin could not be identified in the blood or urine. However, IgG subclass restriction without light-chain restriction is not considered to be monoclonal as it can occur in polyclonal immunoglobulin deposition disease [7]. Antibodies against heavy chain constant domains may be needed in cases of heavy chain deposition disease (HCDD) to look for heavy chain truncation [13]. In some cases, additional studies are required to identify the nature of deposits, such as immunoelectron microscopy or laser microdissection followed by mass spectrometry [14–17].

Hematological workup is crucial for clonal identification because the same kidney lesion can occur in different B-cell disorders, and treatment differs according to the plasmacytic or lymphocytic nature of the clone. Bone marrow aspiration and biopsy are required, including the use of sensitive techniques (flow cytometry, molecular analysis) to better identify small clones [7]. Peripheral blood flow cytometry is helpful in identifying clones of chronic lymphocytic leukemia or monoclonal B-cell lymphocytosis [18].

Extrarenal manifestations can occur in some monoclonal immunoglobulin-related kidney diseases and may be clinically significant. It is important to identify the involvement and impairment of the extrarenal organs so these can be managed appropriately. Cardiac evaluation with echocardiogram and cardiac biomarkers such as N-terminal pro-brain natriuretic peptide (NT-proBNP) and troponin T are standard of care in patients with Ig-related amyloidosis [19, 20]. This is also recommended in patients with MIDD that have cardiac-related symptoms [21]. Liver involvement can be detected by liver function test and imaging studies. Nerve involvement is not uncommon in amyloidosis and can involve both peripheral nerves and the autonomic nervous system [20]. Assessment of these impairments is important as it can affect therapeutic strategies by altering drug elimination and tolerability of adverse effects [22].

Because paraprotein-associated renal disorders are heterogeneous, management requires collaborative work between hematologists and nephrologists. Early diagnosis and efficient chemotherapy targeting the causal B-cell clone are mandatory to improve renal prognosis and patient survival [22].

Pathophysiology

The kidney disease may complicate an already diagnosed clonal B-cell disorder or reveal a previously unknown hematological disease. Renal disease in B-cell lymphoproliferative disorders may result from two main pathophysiological mechanisms that can even coexist in the same patient, i.e. the intrinsic nephrotoxicity of the secreted monoclonal immunoglobulin and malignant infiltration of the renal parenchyma by malignant B-cells, which will not be addressed further in this chapter. The physicochemical properties of monoclonal immunoglobulin appear to be the main determinant of their nephrotoxicity as well as influencing the topography and pattern of kidney lesions. Deposition of all or part of the monoclonal immunoglobulin is the most common mechanism and this can occur in various ultrastructural patterns (amorphous, crystalline, fibrillar, or microtubular) of deposits or inclusions. Other mechanisms include complement activation, autoantibody activity or cytokine secretion induced by the monoclonal immunoglobulin (Table 29.1) [10, 39].

Nephrotoxic Monoclonal Free Light Chains

Several mechanisms of nephrotoxicity of free light chains (FLCs) have been described. These include extracellular deposition in AL amyloidosis (organized deposits) and light-chain deposition disease (LCDD) (nonorganized deposits), and precipitation/crystallization in cast nephropathy and light-chain proximal tubulopathy [8, 40]. Under physiological conditions, polyclonal FLCs, as other low molecular weight proteins, are freely filtered by the glomerulus and reabsorbed in proximal tubular cells by the megalin/cubilin multiligand receptor complex [41]. FLCs are then degraded in endolysosomal vesicles and only a minute amount is present in the final urine [42]. During symptomatic multiple myeloma large amounts of monoclonal FLCs are filtered by the glomerulus, overwhelming the reabsorption capacity of the endocytic receptors megalin/cubilin in the proximal tubule. This allows the monoclonal FLCs to flow into the loop of Henle. Cast nephropathy results from the interaction of these FLCs with uromodulin (Tamm–Horsfall protein) in lumen of the thick ascending limp of the loop of Henle, leading to tubular obstruction and acute kidney injury (AKI). Uromodulin is the most abundant protein excreted in the urine under physiological conditions, but its complete

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Table 29.1 Summary of the main pathological and hematological findings in paraprotein associated renal disorders.

Localization of renal lesions	Kidney disease	Mechanism of renal toxicity	Ultrastructural appearance	Characteristics of monoclonal gammopathy	Reference
Glomerular	Ig-related amyloidosis	Deposition	Fibrils	λ > κ, IgM<10% in AL amyloidosis Truncated γ in AH amyloidosis LC + truncated HC in AHL amyloidosis	[19, 23]
	MIDD	Deposition	Nonorganized	κ > λ in LCDD (usually Vκ1 or Vκ4) Truncated HC (mostly γ) in HCDD LC + truncated HC in LHCDD	[13, 21, 24]
	PGNMID	Deposition	Nonorganized	Mostly IgG3 (κ > λ)	[25]
	Immunotactoid GN	Deposition	Microtubules	Mostly IgG1 (κ > λ)	[26, 27]
	Type I cryoglobulinemia	Deposition/precipitation	Microtubules/crystals	Mostly IgG or IgM	[28]
	Type II cryoglobulinemia	Deposition	Curved short tubular structures Nonorganized	IgM acting as a rheumatoid factor	[12]
	C3 glomerulopathy	CAP activation		IgG	[29–31]
Tubular	Cast nephropathy	Precipitation	Crystals	κ > λ	[4, 32]
	Proximal tubulopathy	Precipitation	Mostly crystals	κ (>90%, mostly Vκ1)	[33, 34]
	Cristal-storing histiocytosis	Precipitation	Crystals	κ	[35, 36]
Vascular	Thrombotic microangiopathy	CAP activation or cytokine mediated or unknown	Microvascular endothelial cell injury	IgG in atypical hemolytic-uremic syndrome IgA = 50% in POEMS syndrome (λ ~ 100%)	[37, 38]

AL, amyloid light chain; AH, amyloid heavy chain; AHL, amyloid light and heavy chain; CAP, complement alternative pathway; HC, heavy chain; HCDD, heavy chain deposition disease; Ig, immunoglobulin; LC, light chain; LCDD, light chain deposition disease; LHCDD, light and heavy chain deposition disease; MIDD, monoclonal immunoglobulin deposition disease; PGNMID, proliferative glomerulonephritis with monoclonal immunoglobulin deposits; POEMS, polyneuropathy-organomegaly-endocrinopathy-monoclonal protein-skin changes; Vκ, variability subgroup of kappa light chain.

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function remains incompletely understood [43]. The binding affinity of FLCs for uromodulin is influenced by the molecular structure of the third complementarity-determining region (CDR3) that specifically recognizes a nine amino-acid domain of uromodulin [44–47]. Facilitating factors that increase light-chain precipitation and/or their interaction with uromodulin have been well described in conditions such as dehydration, hypercalcemia, nonsteroidal drug use, furosemide, and acidic urine [48–50]. Kidney injury in cast nephropathy is also perpetuated by interstitial inflammation and fibrosis induced by the monoclonal FLCs. In vitro studies and animal experiments have shown that excessive endocytosis of myeloma light chains triggers oxidative stress, activation of NF-κB, and release of inflammatory mediators (IL-6, IL-8, MCP-1, and TGF-β) leading to tubulo-interstitial inflammation, fibrosis, and morphologic alteration of the tubular epithelium [48, 51, 52].

Most other types of kidney injury related to pathogenic light chains occur in patients with small B-cell or plasma cell clones with low amounts of monoclonal immunoglobulin [6, 10]. In this context, the kidney toxicity is not driven by the tumor burden but is related to structural peculiarities of the monoclonal FLC [8]. For example, light-chain proximal tubulopathy is mostly related to kappa light chains that are restricted to the Vκ1 subgroup and derive from only two germline genes (Vκ1-33 and Vκ1-39). Some mutations in the variable domain confer a resistance to proteolysis, leading to the formation of crystals within the endolysosomal compartment of proximal tubular cells [53]. Accumulation of these light chains in proximal tubules inhibits receptor-mediated endocytosis and provokes urinary leak of phosphate, uric acid, glucose, amino acids, and low-molecular-weight proteins, with proximal (type 2) renal tubular acidosis [54]. On the other hand, most light chains involved in renal AL-amyloidosis are derived from two germline Vλ genes (Vλ6-57 and Vλ3-1), but no common structural peculiarities have been identified. However, germline gene usage influences the organ tropism with predominant kidney involvement in Vλ6-57 patients and more common cardiac involvement in Vλ1-44 patients [55–57]. Structural peculiarities of light chains have been also reported in LCDD with overrepresentation of the Vκ4 and Vκ1 subgroup of variability, abnormal glycosylation, and high isoelectric point values of variable domain complementarity determining regions, possibly accounting for tissue deposition along the anionic proteoglycans of the basement membranes [21, 58–61].

Nephrotoxic Monoclonal Free Heavy Chains

The deposition of free monoclonal heavy chains is a rare condition seen in AH amyloidosis and HCDD. The most striking feature of deposited heavy chains is the deletion of the first constant (CH1) domain [13, 62, 63]. The nephrotoxic heavy chain is often undetectable by electrophoresis and immunofixation. In this context, immunoblotting is a useful technique to detect small amounts of truncated heavy chains. However, this technique is not widely available. In HCDD, cationic charges of the heavy chain variable domain probably favor the formation of amorphous deposits along renal basement membranes [13].

Nephrotoxic Monoclonal Entire Immunoglobulins

Mechanisms of toxicity of entire immunoglobulins in PGNMID, immunotactoid glomerulonephritis, and cryoglobulinemic glomerulonephritis are poorly understood. These disorders are mostly induced by monoclonal IgG1 or IgG3 known to induce complement activation through the classical pathway [9, 39]. Immunoglobulin deposits usually coexist with C3 and sometimes C1q and C4 deposits [64, 65]. Complement activation through the classical, lectin or alternative pathway is probably a main determinant of glomerular hypercellularity and inflammation in these disorders. Experimental studies in mice have shown that in cryoglobulinemic glomerulonephritis the pattern of kidney lesions depends on peculiarities of the molecular structure of pathogenic IgG [66, 67].

Complement and Cytokine Activation Associated with Monoclonal Gammopathy

Recent studies have shown that the incidence of monoclonal gammopathy in patients >50 years old with C3 glomerulopathy is high [29, 68–70]. This association is not fortuitous as suggested by the presence in some cases of autoantibody activity against CAP regulatory proteins (anti-factor H antibody and C3Nef) and by the beneficial effect of clone-directed therapy [30]. However, the mechanism of complement activation is different in the majority of patients and may involve bystander polyclonal antibodies directed against CAP regulatory proteins or direct activation of the CAP by the monoclonal immunoglobulin [71]. Cytokine activation is probably involved in thrombotic microangiopathy-like lesions in polyneuropathy, endocrinopathy, organomegaly, monoclonal gammopathy, and skin changes (POEMS) syndrome. This disease is characterized by striking elevation of serum vascular endothelial growth factor (VEGF) levels that probably account for glomerular endothelial cell injury [37, 72].

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Diagnosis

Tubulointerstitial Lesions

Light-chain Cast Nephropathy

AKI is present at diagnosis in approximately 30% of patients with symptomatic multiple myeloma. AKI is mostly related to light-chain cast nephropathy, a myeloma defining event invariably associated with high tumor mass [73]. Apart from multiple myeloma, light-chain cast nephropathy has been also described in Waldenström macroglobulinemia, chronic lymphocytic leukemia, and other lymphomas [64, 74–77]. Patients with cast nephropathy typically present with severe AKI, sometimes requiring dialysis. AKI is isolated or associated with general symptoms related to high tumor mass such as skeletal pains related to lytic bone lesions. Urine protein electrophoresis typically shows prominent light-chain proteinuria with albuminuria <10% [78, 79]. In around 50% of patients, cast nephropathy is triggered by facilitating factors, namely dehydration, hypercalcemia, infection, or nephrotoxic drugs (nonsteroidal anti-inflammatory agents, diuretics, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers) [32, 78, 80]. The use of modern contrast media has not been associated with cast nephropathy in recent large series [78]. The risk of cast nephropathy is influenced by the amount of monoclonal light chains excreted in the urine and is particularly high when light-chain proteinuria exceeds 2 g/day [81].

Histologically, the cast nephropathy is defined by the presence of periodic acid Schiff (PAS) stain negative and fractured casts in distal tubule lumina, often with crystalline appearance and usually accompanied by giant cell reaction and tubulorrhexis (Figure 29.1). Severe interstitial inflammation is often present and plays a role in the development of irreversible fibrosis and chronic kidney injury. The presence of numerous casts has been found to be predictive of a poor renal prognosis [32]. On immunofluorescence, the casts stain brightly with anti-kappa or anti-lambda antibody. Ultrastructural examination reveals the crystalline organization of the casts [12].

Light-chain Proximal Tubulopathy

Light-chain proximal tubulopathy rarely occurs in the context of symptomatic multiple myeloma or overt lymphoid malignancy, and most cases fall into the spectrum of MGRS [33, 82]. The frequency is low and light-chain proximal tubulopathy represents 5% of Ig-related renal diseases. The median age at diagnosis is around 60 years, with a slight male predominance [33, 34]. Patients typically present with slowly progressive chronic kidney failure with tubular proteinuria and Bence Jones proteinuria usually of kappa isotype. The presence of hypouricemia and hypophosphatemia must encourage further explorations to detect proximal tubule dysfunction. However, signs of tubular dysfunction may be absent in patients with more advanced kidney impairment. The complete form of proximal tubulopathy, referred to as light-chain associated Fanconi syndrome, is defined by the urinary leak of low molecular weight proteins, phosphate, uric acid, glucose, and amino acids. Patients who exhibit only some of these features are considered to have a partial Fanconi syndrome. Patients may also present with prominent bone symptoms, including stress fractures, secondary to hypophosphatemic osteomalacia [33, 83]. Thus, searching for monoclonal gammopathy is mandatory in adults with symptoms of proximal tubule dysfunction.

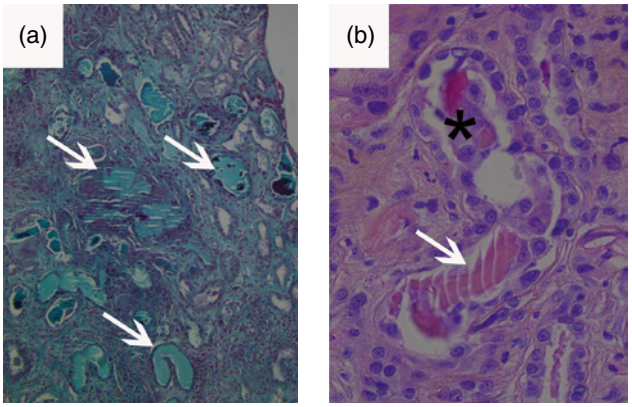

Figure 29.1 Myeloma cast nephropathy by light microscopy. (a) Masson's trichrome staining (×200). Representative example of cast nephropathy with numerous typical polychromatophilic and fractured casts (arrows) associated with interstitial fibrosis and inflammation. (b) Hematoxylin and eosin staining (×400). Typical cast (arrow) with giant cell (asterisk) and tubulorrhexis.

The kidney biopsy shows typically rhomboid-shaped hypereosinophilic and PAS-negative crystals within proximal tubular cells. Their detection by light microscopy is sometimes difficult, highlighting the diagnostic value of immunofluorescence and ultrastructural examination, which should be systematically considered in the presence of suggestive lesions such as focal proximal tubule dedifferentiation and atrophy (Figure 29.2) [33, 84, 85]. In some cases, antigenic epitopes normally recognized by antibodies routinely used may be sequestered by the crystalline lattice, resulting in false negative results. Ancillary techniques are then needed, including immunofluorescence on paraffin-embedded tissue after protease digestion or immunoelectron microscopy [85, 86]. Light-chain proximal tubulopathy may also manifest with accumulation of light chains within proximal tubular cells without crystal formation. These patients often present with evidence of tubular injury, but Fanconi syndrome is rare [34, 87, 88].

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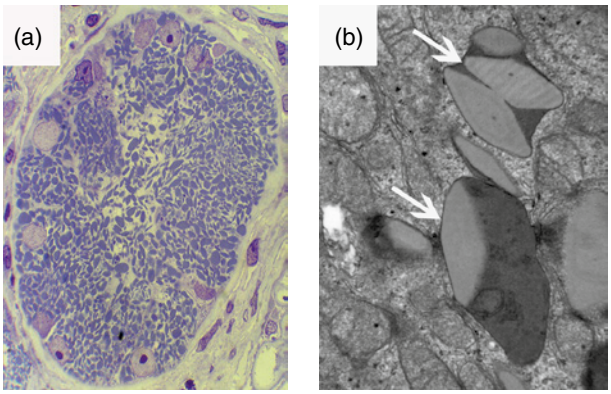

Figure 29.2 Kappa light chain proximal tubulopathy. (a) Light microscopy (toluidine blue staining, ×1000). Patient with massive cytoplasmic crystalline accumulation in proximal tubular cells. (b) Electron microscopy (×50 000). Abundant rhomboid crystals (arrows) surrounded by a single membrane within the cytoplasm of proximal tubular cells.

Crystal-storing Histiocytosis

Crystal-storing histiocytosis is a rare complication of symptomatic myeloma or MGRS, defined by the accumulation of light-chain crystals in histiocytes. These histiocytes are commonly seen in the bone marrow but can be found in other sites such as kidney, perirenal fat, lungs, cornea, and joints. Crystal-storing histiocytosis may coexist with light-chain proximal tubulopathy and/or cast nephropathy [35, 36].

Glomerular Lesions

Glomerular Disorders with Organized Immunoglobulin Deposits

Immunoglobulin-related Amyloidosis

Immunoglobulin-related amyloidosis is the most common glomerular lesion associated with monoclonal gammopathy [23]. The average age at diagnosis is 65 years, with a slight male predominance (approximatively 60% of cases). Among this group, AL-amyloidosis is the most frequent subtype where amyloid is composed of monoclonal light chains (usually lambda). In rare cases, immunoglobulin-related amyloidosis is derived from fragments of heavy chains and light chains (AHL) or heavy chains only (AH). AL-amyloidosis is the prototype of MGRS, since most patients present at diagnosis with an isolated monoclonal gammopathy or indolent B-cell clone [9]. Progression to symptomatic myeloma is unusual [89, 90]. AL-amyloidosis complicates lymphoplasmacytic proliferation with secretion of monoclonal IgM in less than 10% of patients [91, 92]. The diagnosis of amyloidosis is based on the demonstration of Congo-red deposits with dichroism and birefringence under polarized light [93]. Since more than 35 proteins have been described as amyloidogenic precursors, characterization of the native protein is the cornerstone of management. Immunofluorescence analysis of frozen tissues, using anti-light and anti-heavy chain antibodies should be preferred to immunohistochemistry, which has lower diagnosis sensibility and specificity [94]. Minimally invasive biopsies (salivary glands, abdominal fat) should be performed as first-line. When tissue biopsies fail to demonstrate amyloid deposition or are insufficient for amyloid typing, biopsy of a clinically affected organ (kidney, liver, gastrointestinal tract, or endomyocardial tissue) should be considered. When a kidney biopsy is performed in patients with renal involvement, it allows characterization of amyloid deposits in most cases (Figure 29.3). The incidence of bleeding complications in systemic AL-amyloidosis after kidney biopsy appears acceptable when performed by experience physicians [95]. Deposits that stain positive for lambda light chain in most cases, predominately in the mesangium and along the glomerular basement membranes, are often associated with interstitial and vascular deposits. Electron microscopy may be useful to confirm the presence of amyloid deposits, particularly in earlier disease stages, and typically shows randomly arranged fibrils of 7–10 nm in external diameter that initially predominate in the external aspect of the glomerular basement membrane. When the nature of the deposits remains indeterminate with routine technics, additional explorations must be carried out, such as immunoelectron microscopy or mass spectrometry after laser microdissection. [9]

All organs can be affected in immunoglobulin-related amyloidosis. Kidney involvement is the most frequent, found in two-thirds of patients at diagnosis. The heart is the most common extrarenal organ involved followed by peripheral nerves and liver. Macroglossia, periorbital purpura or skeletal muscle pseudohypertrophy are particularly suggestive symptoms but are rarely present [19]. Renal manifestations include glomerular symptoms in most cases with abundant proteinuria predominantly composed of albumin, usually without hematuria or hypertension. Nephrotic syndrome and chronic kidney disease (CKD) are observed in approximately 50% of cases at diagnosis. When the deposits are predominantly tubulointerstitial and vascular, chronic interstitial nephritis with polyuria due to defective urine concentration ability and slowly progressive CKD with little proteinuria is possible [96]. Organ involvement in systemic AL amyloidosis is now defined by consensus criteria, updated at the 2010 meeting of the International Society of Amyloidosis in Rome [20].

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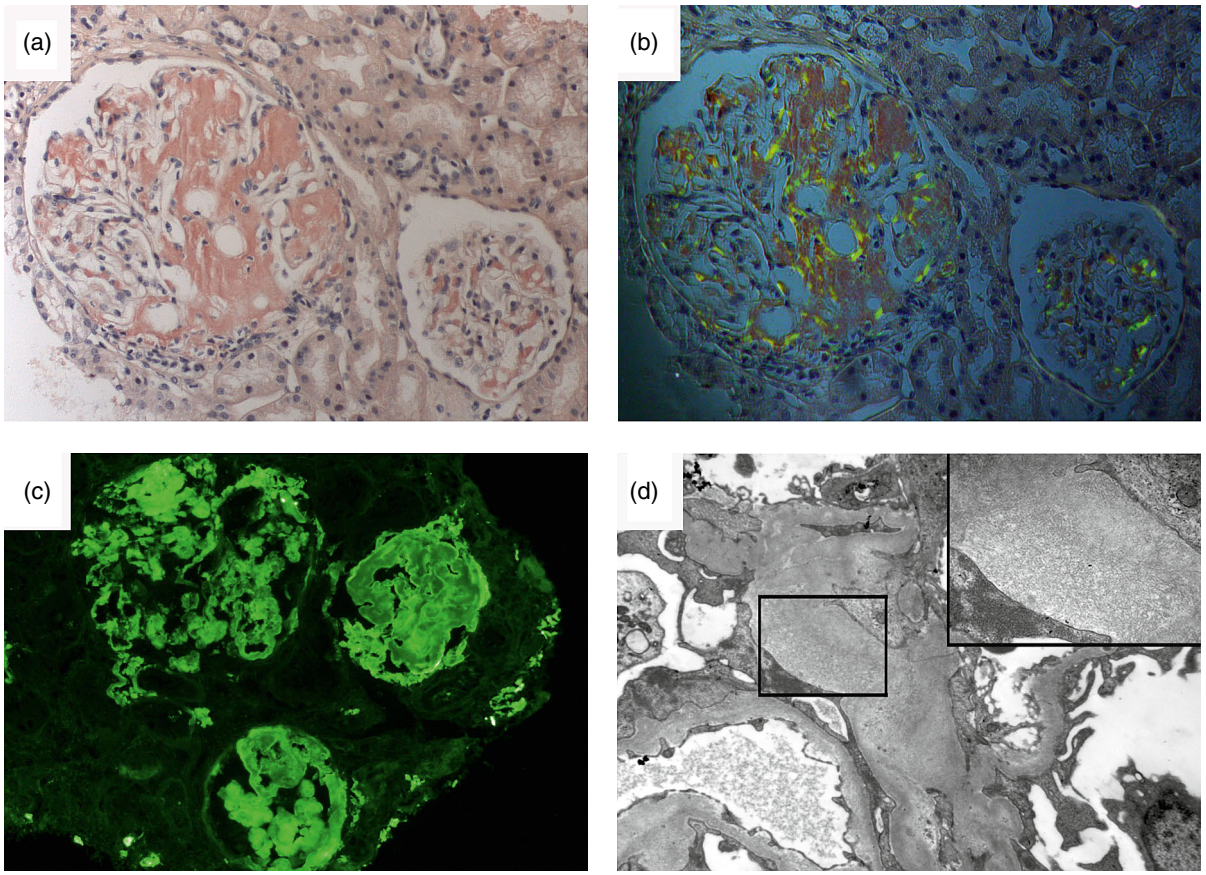

Figure 29.3 AL-amyloidosis. (a and b) Light microscopy (Congo red staining, ×200). Glomerular mesangial and capillary wall Congo red positive deposits (a) with characteristic dichroism and apple green birefringence under polarized light (b). On immunofluorescence (×200) glomerular amyloid deposits stain brightly for lambda light chain (c) with negative staining for kappa light chain (not shown). (d) By electron microscopy (×12 000, insert ×50 000), amyloid deposits are composed of haphazardly oriented fibrils ranging from 7 to 14 nm in diameter.

Immunotactoid Glomerulonephritis

Immunotactoid glomerulonephritis, also referred to as glomerulonephritis with organized microtubular monoclonal immunoglobulin deposits (GOMMID), is a very rare entity (fewer than 100 cases in the literature) characterized by Congo red negative deposits that show typical ultrastructural organization into microtubules of 10–60 nm in external diameter, with a distinct hollow core at magnification of less than 30 000. By definition, cryoglobulin testing should be negative. Deposits are monotypic by immunofluorescence, mostly composed of IgG1κ, usually associated with C3. Light microscopic appearance is not specific, but membranous nephropathy or membranoproliferative glomerulonephritis patterns are commonly observed (Figure 29.4). Most patients present with nephrotic range proteinuria, hematuria, kidney insufficiency, and hypertension. Immunotactoid glomerulonephritis has been mostly reported in patients with MGRS or chronic lymphocytic leukemia with an average age of 60 years [26, 27, 97].

Cryoglobulinemic Glomerulonephritis

Cryoglobulins are immunoglobulins that precipitate under cold exposure. Three types exist but only two contain monoclonal immunoglobulin. Type 1 is composed of a single type of monoclonal immunoglobulin (usually IgG or IgM) and type 2 (mixed) contains classically a monoclonal IgM acting as a rheumatoid factor against polyclonal IgG [98]. The underlying condition is plasma cell dyscrasia or lymphoproliferative disorder, particularly lymphoplasmacytic lymphoma. Type II mixed cryoglobulinemia is observed in around 10% of patients with chronic virus C infection. Glomerulonephritis is more common with type II cryoglobulinemia. Median age is 62 years old and it is more common in women. [28] Renal presentation includes classically proteinuria and microscopic hematuria, sometimes with moderate chronic kidney insufficiency. Severe hypertension is commonly observed. Some patients may present an acute nephritic syndrome characterized by hematuria,

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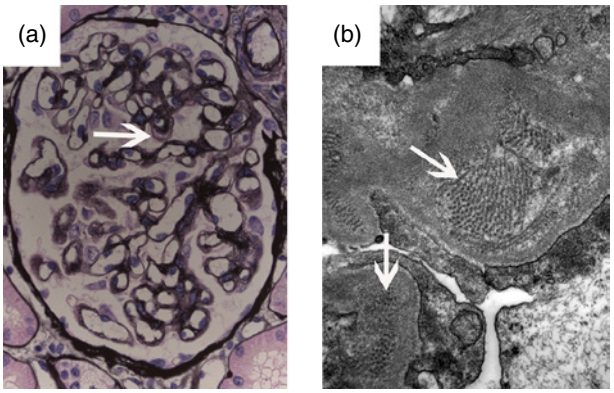

Figure 29.4 Immunotactoid glomerulonephritis. (a) Light microscopy (Marinozzi's silver staining, ×400). Membranous pattern of injury associated with focal duplication of glomerular basement membranes (arrow). (b) By electron microscopy (×50 000), the deposits are composed of microtubules with hollow centers and organized in parallel arrays (arrows).

usually macroscopic, severe proteinuria and hypertension, and acute kidney failure. Extrarenal manifestations are common and often present as purpura, ulcers, peripheral neuropathy, and arthralgia [28]. On light microscopy (Figure 29.5a,b), cryoglobulinemic glomerulonephritis shows membranoproliferative or endocapillary proliferative glomerulonephritis with intracapillary infiltrating monocytes and large PAS-positive intraluminal immune deposits (thrombi). Careful immunofluorescence analysis is crucial to determine the type of cryoglobulinemia, as both IgM and IgG are present in type 2 cryoglobulinemia without clear light-chain restriction due to the presence of polyclonal IgG. By electron microscopy (Figure 29.5c), deposits predominate in the subendothelial space and intracapillary lumen, and appear focally organized (microtubular or "fingerprint" substructure) [9].

Glomerular Disorders with Nonorganized Immunoglobulin Deposits

Monoclonal Immunoglobulin Deposition Disease

Randall-type MIDD is the most common glomerulopathy with nonorganized deposits. MIDD commonly occurs in the context of a plasma cell disorder with criteria for symptomatic multiple myeloma in nearly 25% of cases and for MGRS (including smoldering myeloma in around 25% of patients) in the remaining patients [21, 24, 99]. The diagnosis is made on approximately 0.5% of kidney biopsies on native kidneys. It is usually discovered around the age of 60 years, with a slight male predominance [21, 24, 100]. According to the composition of deposits, three categories are distinguished: LCDD, HCDD, and light- and heavy-chain deposition disease (LHCDD). MIDD is characterized by linear nonorganized Congo red-negative monoclonal immunoglobulin deposits along basement membranes [9]. As immunoglobulin-related amyloidosis, MIDD is a systemic disease with prominent kidney manifestations, but heart, liver, or peripheral nerve involvement may be encountered [21]. In the kidney, deposits are invariably observed along tubular basement membranes, and in most cases in the mesangium, glomerular basement membranes, and around arteriolar myocytes. The most common histologic feature is glomerulosclerosis mimicking diabetic nephropathy (Figure 29.6). The usual presentation is progressive kidney failure and glomerular symptoms, including nephrotic

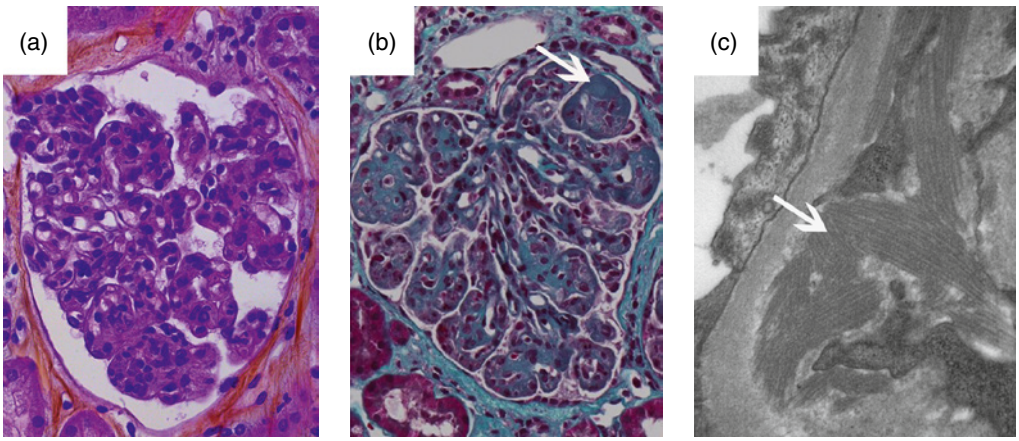

Figure 29.5 Cryoglobulinemic glomerulonephritis. (a and b) Light microscopy. (a) Hematoxylin and eosin staining, ×400. Membranoproliferative glomerulonephritis pattern of injury characterized by mesangial expansion and hypercellularity and duplication of glomerular basement membranes. (b) Masson's trichrome staining, ×400. Intracapillary immune deposits suggestive of thrombi (arrow), the hallmark histologic finding of cryoglobulinemic glomerulonephritis. (c) By electron microscopy (×50 000), the deposits predominate in the subendothelial space with focal microtubular organization (arrow).

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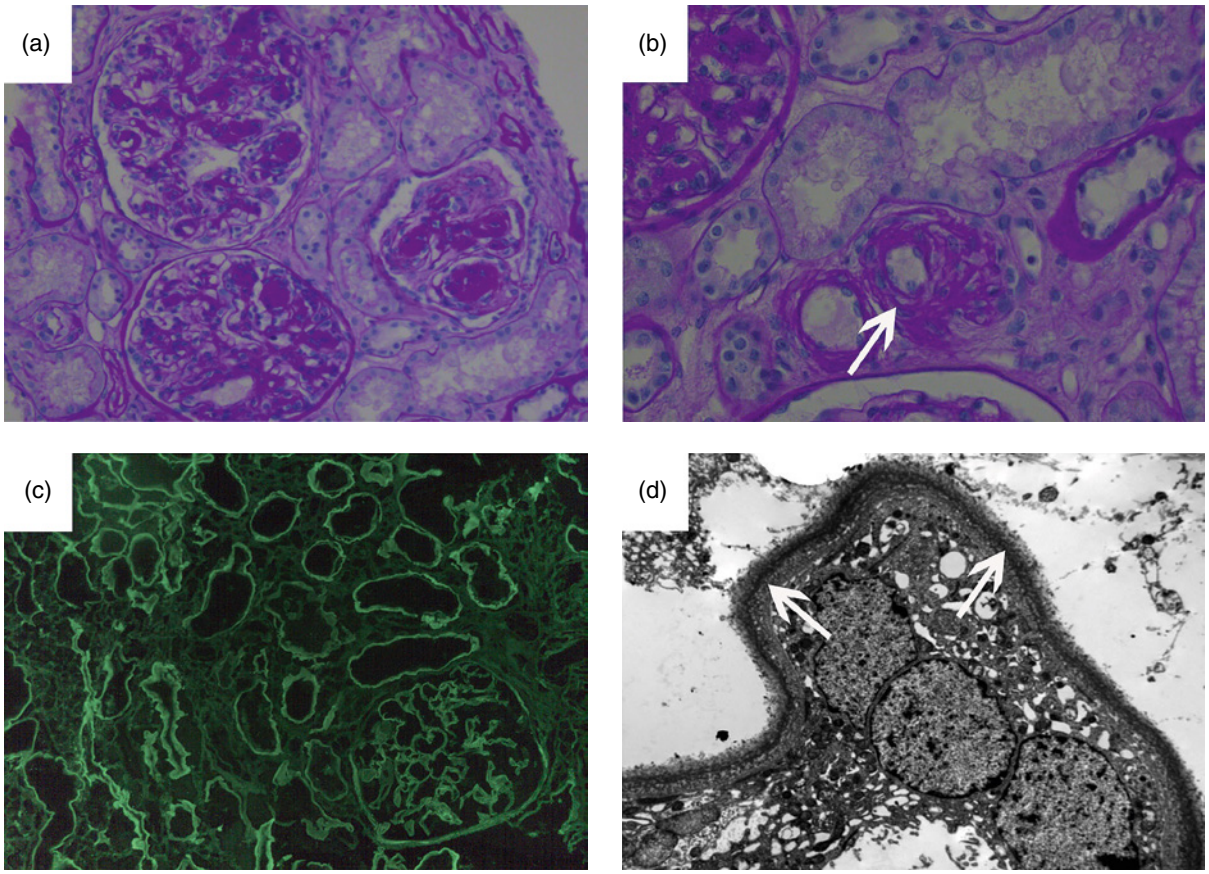

Figure 29.6 Light-chain deposition disease. (a and b) Light microscopy (periodic acid Schiff staining, ×400). Section of renal cortex showing nodular glomerulosclerosis with nodular mesangial deposits and aneurysmal dilatation of the capillary lumens (a). Vascular deposits around arteriolar myocytes (arrow) (b). (c) Immunofluorescence microscopy (anti-κ fluorescein isothiocyanate conjugate, ×200). Linear deposits along glomerular and tubular basement membranes, and around vascular myocytes. (d) Electron microscopy (×15 000). Enlarged multilayered tubular basement membrane with electron-dense (arrows) powdery punctuate deposits predominating in the outer aspect.

syndrome in half of patients. Uncommonly, MIDD may manifest with slowly progressive kidney disease without significant proteinuria. In this context, glomerulosclerosis is uncommon and deposits predominate in the renal vascular and tubular compartments [101, 102]. LCDD occurring in the context of symptomatic multiple myeloma usually coexists with cast nephropathy and has similar presentation and outcome as pure cast nephropathy [21].

Proliferative Glomerulonephritis with Monoclonal Immunoglobulin Deposits

PGNMID is a rare glomerular disorder defined by nonorganized immunoglobulin (most commonly IgG3) and complement component deposits in the glomerular capillary walls and mesangium, mimicking an immune complex-mediated glomerulonephritis (Figure 29.7). Around 100 cases are reported in the literature. The average age at diagnosis is 55 years old. Multiple myeloma is rare and around two-thirds of patients have no detectable monoclonal component by standard techniques [25, 103]. PGNMID appears as a renal limited disorder with prominent glomerular symptoms and frequent CKD. The risk of recurrence after kidney transplantation has been reported to be as high as 90% [104].

Glomerular Disorders without Immunoglobulin Deposits

C3 Glomerulopathy Associated with Monoclonal Gammopathy

C3 glomerulopathy regroups two entities characterized by glomerular C3 deposition without immunoglobulin: C3 glomerulonephritis and dense deposit disease. Both entities are associated with dysregulation of the CAP. By electron microscopy, dense deposit disease is distinguished from C3 glomerulonephritis by the presence of characteristic "sausage-shaped" intramembranous electron dense deposits [105]. Patients typically present with glomerular

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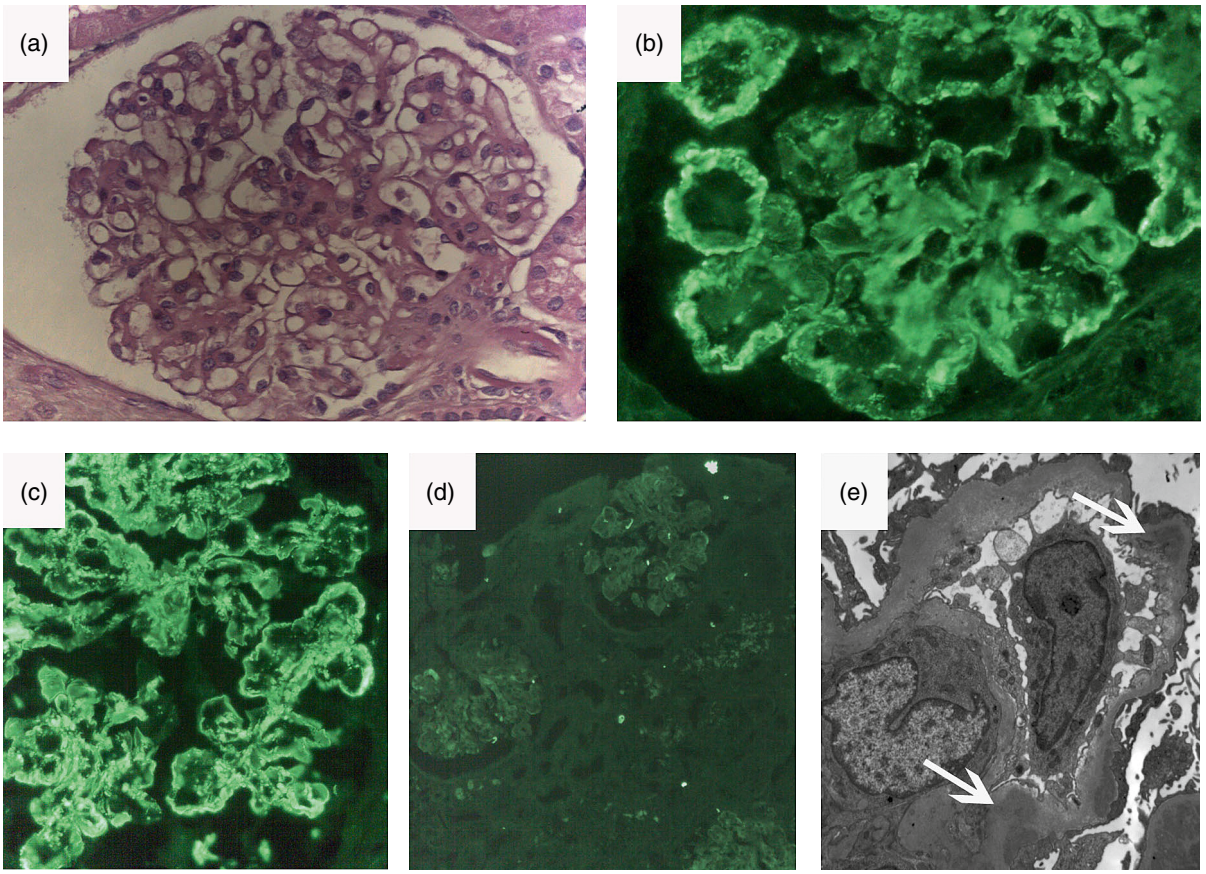

Figure 29.7 Proliferative glomerulonephritis with monoclonal immunoglobulin deposits. (a) Light microscopy (hematoxylin and eosin staining, ×400). Membranoproliferative glomerulonephritis with global mesangial and segmental endocapillary hypercellularity. (b–d) Immunofluorescence microscopy. Mesangial and glomerular capillary wall staining for IgG3 (b) and kappa (c). Negative staining for lambda (d). (e) Electron microscopy (×15 000). Granular nonorganized electron-dense deposits (arrows) predominant in the subendothelial space of glomerular basement membrane.

symptoms (proteinuria and hematuria) and progressive CKD. In patients over 50 years of age, most cases of C3 glomerulopathy are associated with a circulating paraprotein [29, 31, 68, 70]. Although direct evidence of a link between monoclonal gammopathy and C3 glomerulopathy is lacking in most patients, the implication is suggested by the presence in some cases of autoantibody activity of the monoclonal immunoglobulin against CAP regulatory proteins and by the beneficial effect on renal outcome of a clone-directed therapy [30, 70].

Thrombotic Microangiopathy Associated with Monoclonal Gammopathy

The term "thrombotic microangiopathy" refers to a diverse group of disorders linked by a common histologic finding of endothelial cell injury. Two categories associated with monoclonal gammopathy have to be distinguish: (i) microangiopathy with hemolytic anemia (MAHA) which can occur in patients with MGRS, symptomatic multiple myeloma, and Waldenström macroglobulinemia, and (ii) glomerular microangiopathy associated with POEMS syndrome where hemolysis and thrombocytopenia are absent [7].

Treatment

Indication of Therapy

Indication of therapy in MGRS is driven by renal damage due to the nephrotoxic immunoglobulin produced by the clone. Therapy in MGRS aims to improve renal survival and in selected patients to reduce the risk of recurrence after renal transplantation. Treatment decisions should also take into account the presence of extrarenal manifestations and the patient's status [22]. Light-chain cast nephropathy seen only in malignant disease is not MGRS and treatment is a medical emergency [106, 107].

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Clone-directed Therapy

The current therapeutic approach in MGRS is to eradicate the underlying B-cell clone with chemotherapy. If the clone is plasmacytic, usually secreting a monoclonal IgG, IgA, or light chain, treatment should be based on antimyeloma agents. The strategy mainly relies on bortezomib, usually combined with an alkylating agent and dexamethasone (CyBorD regimen) that produces rapid and deep hematological response. Bortezomib is easy to use in patients with impaired renal function since it does not require dose adaptation. High-dose melphalan followed by autologous stem cell transplantation (ASCT) may be a therapeutic option in some patients with plasma cell clone. However, mortality and morbidity related to ASCT increase in patients with renal impairment, and some patients may worse their renal function during the procedure. Since melphalan is eliminated by renal excretion, dose adaptation is needed in patients with CKD stage 3 or above. In case of relapsing or refractory disease, immunomodulatory drugs should be considered. Lenalidomide must be used with caution in patients with renal dysfunction since this drug is predominantly eliminated through renal excretion and may sometimes worsen renal function with unclear mechanism, particularly in patients with AL amyloidosis [108]. Thalidomide and pomalidomide are probably more appropriate since they do not require dose adaptation. Anti-CD38 monoclonal antibodies, which are highly effective in symptomatic multiple myeloma and are currently being evaluated in AL amyloidosis, are likely to be increasingly used in the treatment of various MGRS [10, 22]. If the clone is lymphoplasmacytic (usually producing a monoclonal IgM) or lymphocytic, the treatment should be based on rituximab-containing regimens [22]. The choice and modality of chemotherapy in light-chain cast nephropathy remains to be defined. The goal of therapy is to rapidly reduce the rate of production of FLCs, a key factor to induce renal response [106, 107]. The use of high-dose steroids seems mandatory because of their anti-inflammatory properties. Bortezomib-based therapy is associated with high rate of renal response in light-chain cast nephropathy[109].

Symptomatic Measures

Cast Nephropathy

Symptomatic treatment is a key step in the management of cast nephropathy. It is based on the rapid correction of precipitating factors such as treatment of infection with non-nephrotoxic antibiotics and correction of hypercalcemia using bisphosphonates despite their potential nephrotoxicity. Hydration is essential with administration of hypotonic (half normal) saline to reduce aggregation of Tamm–Horsfall protein and its interaction with urine FLC [106, 107]. The use of adjuvant supportive measures to rapidly reduce the level of FLCs is still debated. Two randomized trials using high cutoff (HCO) dialyzer for the removal of serum FLC produced different results in terms of renal recovery. The European trial (EuLITE) had randomized patients to a standard dialysis with a high-flux dialyzer versus extended dialysis using a HCO dialyzer in addition to bortezomib-based triplet chemotherapy. In this study a similar hemodialysis independence rate (60%) was observed in both groups [110]. The French randomized clinical trial with biopsy-proven cast nephropathy reported that intensive HCO hemodialysis does not significantly increase early hemodialysis-independence rate but results in significantly higher 6 and 12 month-renal recovery rates compared to intensive hemodialysis with conventional high-flux dialyzers [78]. Further larger studies are needed to confirm the benefice of extracorporeal removal of FLCs in light-chain cast nephropathy.

Ig-related Amyloidosis

Symptomatic measures, adapted to organ failures, are essential in the management of Ig-related amyloidosis. In patients with nephrotic syndrome, fluid retention and edema require treatment with loop diuretics often given at a high dose or combined with other diuretics. Caution is required in the use of standard treatment of cardiac failure in patients with amyloidosis. Calcium inhibitors, β-blockers, and digitalis are to be avoided due to excess toxicity. Amiodarone should be considered as first-line therapy for arrhythmia. Angiotensin converting enzyme inhibitors can promote hypotension and are often poorly tolerated. In patients with severe, life-threatening cardiac involvement, pacemaker or defibrillator implantation may be required [19, 90].

Other Glomerular Disorders

As in other glomerulonephritis, the use of angiotensin converting enzyme inhibitors and/or angiotensin receptor blockers is essential to control blood pressure and to reduce proteinuria.

Proximal Tubulopathy

Symptomatic measures to prevent osteomalacia are mandatory, including phosphate, calcium, and vitamin D supplementation. Prophylaxis against hypokalemia is often necessary [33].

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Kidney Transplantation

Recent advances in chemotherapy result in improved patient survival. Selected patients with CKD stage V are now eligible for renal transplantation. Due to the risk of recurrence, hematological remission seems mandatory before considering a renal transplant [104, 111–113]. The long-term results of renal transplantation in MGRS, particularly the risk of infection and neoplasia, remain to be evaluated.

Conclusion

The spectrum of renal complications associated with paraproteins is heterogeneous and the diagnosis relies on careful examination of biopsy samples by light microscopy, immunofluorescence studies, and in most cases electron microscopy. Identification of the underlying B-cell clone is crucial for treatment strategy.

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Primary Immune Complex-mediated Membranoproliferative Glomerulonephritis and C3 Glomerulopathies: A Clinical Approach

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Introduction

Primary immune complex-mediated membranoproliferative glomerulonephritis (IC-MPGN) and C3 glomerulopathies (C3G) have attracted a substantial body of basic and clinical research in the last decade. This has been mainly due to the recent dynamics in the field of complement study and the development of an increasing number of complement modulators. These nephropathies have been recently reclassified with the individualization of a new subtype, C3 glomerulonephritis (C3GN), and experimental and clinical studies have dissected complement pathway involvement in their pathogenesis. Nevertheless, the rarity of theses renal diseases and the absence to date of prospective controlled trials are clear limitations to an "evidence-based" approach to these glomerulopathies.

Definitions

Primary IC-MPGN is classically defined by peculiar pathology findings in kidney biopsy [1]: (i) on light microscopy study, a mesangial matrix expansion and "double contour" aspects due to a duplication of the glomerular basement membrane, and (ii) on immunofluorescence study, a coexistence, in equal intensity, of immunoglobulins (mainly IgG), and complement components (mainly C3) deposits. IC-MPGN are subdivided in two types: MPGN type I with mesangial and endomembranous immune deposits and MPGN type III with endo and extramembranous immune deposits.

C3G are characterized by exclusive or predominant (≥ 2+ intensity than any other type of deposit) glomerular C3 deposits [2, 3]. C3G are divided into two subtypes based on electron microscopy study findings: C3G with electron-dense deposits in the glomerular (and tubular) basement membrane, called "dense deposits disease" (DDD) [4], and C3G without such deposits, called C3 glomerulonephritis (C3GN) [5]. The precise composition of dense deposits remains elusive. They probably contain complement activation products (C9) but not predominantly C3 [2].

On light microscopy study, C3G display variable patterns of renal pathological findings: a typical aspect of MPGN in half of the cases [6], a "mesangial" pattern (mild expansion of the mesangial matrix, no "double contour") [5], a crescentic pattern [7, 8], and in some instances a pathological presentation very similar to the one noted in acute post-infectious glomerulonephritis (exsudative endocapillary proliferation) [6].

These definitions have several limitations. First, the pathological MPGN pattern is not specific of primary MPGN. It is also encountered in a wide variety of secondary MPGN [9], ranging from systemic disease-associated MPGN (lupus and cryoglobulinemic nephritis, Sjögren's disease nephropathy) to infection-related glomerulopathy (hepatitis C), but also chronic thrombotic microangiopathy or DGK (Diacylglycerol kinase) epsilon-associated nephropathy [10]. Second, the pathological patterns of IC-MPGN and C3G vary from one patient to another but also over time in a given patient in terms of the relative abundance of C3 and Ig deposits [11], but also and more importantly in terms of mesangial, endocapillary, and/or extracapillary proliferation.

Epidemiology

Primary IC-MPGN and C3G are rare types of nephropathy. In a recent series from the United States [12], MPGN types I and III represented between 2.5% and 4.5% of all glomerular

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diseases diagnosed in kidney biopsies. DDD accounted for less than 0.5% of all glomerulopathies. The incidence of these diseases was stable between 1986 and 2015. In another study from the United States [12], less than 0.3% of all patients reaching end-stage renal disease (ESRD) between 1996 and 2013 had MPGN (probably combining IC-MPGN and C3G) as a primary renal diagnosis. C3GN is a more recently (2010) [2, 5] individualized entity and no specific incidence is available.

Pathophysiology

IC-MPGN and C3G are prototypic complement-mediated diseases, with an activation of the complement cascade initiated by distinct mechanisms. On one hand, it is assumed that IC-MPGN results from the deposition in the glomerulus of immune complexes [9] that triggers the activation of the classical complement pathway, starting with activation of C1, C4, and C2 leading to the formation of the classical pathway C3 convertase (C4b2a) which cleaves C3, generates a classical C5 convertase (C4b2a3b), and ultimately leads to the activation of C5 and of the complement terminal pathway. C5b generation leads to the assembly of the membrane attack complex (C5b, 6, 7, 8, 9), which induces cellular injury. IC deposition triggers mesangial cells proliferation, and in some cases tissular injury leads to inflammatory cells influx, release of proteases and reactive oxygen species, capillary wall necrosis, and extracapillary proliferation. "Double contour" aspects have been long been attributed to an expansion of the mesangial matrix that dissociates the two leaflets of the glomerular basement membrane. The pathogenesis of "double contour" may, however, be more complex and is not fully understood.

The assumption that IC deposition is the primary trigger of IC-MPGN is challenged by pathological findings in repeat biopsies in patients with this type of nephropathy. Ig deposits vary widely from one biopsy to another in a given patient and may even disappear following treatment, whereas C3 deposits usually persist [11, 13]. Besides, complement classical pathway activation, exemplified by C4d deposition, has been documented in only few cases of primary IC-MPGN [14]. Finally, patients with IC-MPGN frequently display features of alternative pathway activation (see infra).

On the other hand, C3G is believed to derive from a dysregulation of the alternative C3 convertase in the circulation. C3 convertase (C3bBb) is a key enzyme of the complement alternative pathway (CAP) that cleaves C3, leading to the formation of the C5 convertase and ultimately to the activation of the complement terminal pathway and the generation of the membrane attack complex. The alternative complement pathway is in a state of low-grade continuous activation (rapidly amplified upon infections) and thus requires tight control. This control targets predominantly the C3 convertase with three main inhibitors that prevents the formation of the C3 convertase through the binding and inactivation of the C3b. These inhibitors include complement factor H (CFH), factor I (FI), and membrane-cofactor protein (MCP). The loss of the regulation of this C3 convertase in the circulation leads to an increased release of the C3 degradation products (C3c, Cb, C3d) and their deposition in the kidney. This pathophysiological hypothesis is supported by animal models. Piglets of the Norwegian Yorkshire breed as well as mice deficient in CFH, develop a C3GN reminiscent of the human disease [15, 16]. The CFH−/− mice model has provided valuable insight into the pathogenesis of C3G and its dynamics, particularly regarding the potential clearance of renal complement deposits following the restoration of tight control of the C3 alternative convertase [17].

In patients with C3G dysregulation of the alternative C3 convertase arises rarely (<10% [18]) from inactivating mutations in the genes coding for CFH, FI, or MCP or activating mutations in the genes coding for the two main components of the C3 convertase, C3 and factor B. Nevertheless, C3G and to a lesser extent MPGN patients have a range of autoantibodies that target the alternative complement pathway, particularly the C3 convertase. The most frequent and extensively documented type of autoantibody is the C3 nephritic factor (C3Nef), an IgG that stabilizes and prolongs the half-life of the C3 convertase. More recently, a C5nephrtic factor has been identified that stabilizes the C5 convertase leading to an excessive activation of the C5 and of the complement terminal pathway [19]. Anti-CFH, anti-C3, and anti-factor B antibodies have also been reported in patients with C3G and more rarely IC-MPGN [18, 20, 21].

Clinical Presentation and Outcome

The available data regarding the clinical presentation and outcome of C3G and IC-MPGN derive from retrospective series which included a substantial number of patients in regard of the rarity of the disease. The four largest recent series from France [5], the United States [22], the United Kingdom [23], and Italy [24] included between 80 and 173 patients. Two series included only C3G patients [22, 23] and the remaining two C3G and IC-MPGN cases [5, 24]. What conclusions can be drawn from the published studies?

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First, C3G is a severe renal disease. The median age of affected patients ranges from 12–15 (DDD) to 28 years [5, 22, 24] and 38–40% of affected patients have a disease onset in childhood [18, 23]. It is associated with a nephrotic syndrome in 16–41% of cases and progresses to ESRD in 20–41% of cases after a median follow-up of 28 months to 11 years [18, 20, 22, 24]. In addition, the disease recurs in up to 40–60% of the kidney grafts [18], but some recurrences are subclinical and do not affect the survival of the renal graft. The same severity of disease has been reported in patients with IC-MPGN [24]: 43–65% present with a nephrotic syndrome, 44% progress to chronic kidney disease and up to 40% reach ESRD. Forty-two percent of patients have a recurrence of the nephropathy in the renal graft [18].

The available data indicate that DDD, C3GN as well as IC-MPGN share the same severe renal presentation and outcome. DDD pattern was associated with an increased risk of ESRD in two studies [18, 23] but not in the three remaining ones [22, 24]. Thus, the clinical relevance of the current classification of C3G and IC-MPGN remains debated. This is in keeping with the results of a retrospective study performed by Little and colleagues [25]. The authors retrospectively analyzed 70 cases of DDD and IC-MPGN diagnosed between 1972 and 1995, and thus before the individualization of C3GN. After a mean follow-up of 13 years, 59% of patients progressed to ESRD. The median time to ESRF was 8.3 years. In multivariate analysis, the severity of interstitial fibrosis, crescent formation, and mesangial proliferation was independently associated with ESRD. Age and MPGN type did not predict renal survival. Regarding renal transplantation, younger age at initial diagnosis and the presence of crescents on the biopsy of native kidneys were independently associated with recurrence of the disease in the renal graft in multivariate analysis. MPGN type was not associated with recurrence. Thus, intensity of inflammatory (crescents) and fibrotic changes in the kidney biopsy predict better the renal outcome of MPGN and C3G than the usual pathological classification of C3G and IC-MPGN [11].

Second, the clinical course of the disease is variable from one patient to another and most strikingly in a given patient over time. Most C3G patients present with chronic subacute forms of the disease characterized mainly by persistent nephrotic syndrome and mildly altered renal function, with 40–50% of patients progressing gradually toward ERSD. Some patients experience acute deterioration of their nephropathy (worsening proteinuria and/or renal function) that may be triggered by infections [24, 26] and a minority (8% of C3G cases in one series [22]) present with a rapidly progressing form of the disease [27–30].

Renal Pathological Findings

Renal pathological features are obviously different in each subtype of MPGN. They are also variable from one patient to another within the same subgroup of MPGNs and in a given patient from one kidney biopsy to another [11]. The paradox of these nephropathies is that a renal disease classified as MPGN may not disclose on light microscopy study typical features of MPGN. This is particularly true for C3G. In a recent series from the United States [22], 61% of C3GN and only 35% of DDD cases had an MPGN pattern. Seventeen percent of C3GN and 35% of DDD cases had a mesangial proliferative pattern, and 13% and 15% had a diffuse endocapillary proliferative pattern reminiscent of the one found in acute post-infectious glomerulonephritis. Besides, cellular or fibro-cellular crescents were found in 17% of C3GN cases and 10% of DDD cases. This wide spectrum of pathological findings in C3G has also been outlined by previous studies [23].

IC-MPGN cases also disclose variable patterns of pathological findings. One of the most striking findings is the variability of the relative abundance of C3, C1q, and immunoglobulin (IgM, IgG, and IgA) deposits in repeat biopsies in patients with IC-MPGN [11]. In some instances, IgG deposits may even disappear while C3 deposits persist [31], a finding that may question the pathogenic relevance of immunoglobulin deposits in IC-MPGN. In addition, data documenting an activation of the classical complement pathway by IC within the kidney in patients with IC-MPGN remain scarce. In a study [14], C4d (a marker of alternative pathway activation) staining was assessed in 18 biopsy specimens of immune-complex GN (including three primary IC-MPGN), 30 biopsy specimens of C3GN, and 13 biopsy specimens of post-infectious GN. In 15 out of 18 biopsies of IC-MPGN, bright (2–3+) C4d staining was detected, whereas only six (20%) cases of C3GN had only trace/1+ C4d staining. C4d staining was negative in six (46%) of 13 biopsies of acute postinfectious glomerulonephritis.

Laboratory Work-up

Complement Assays

C3G is a prototypic complement-mediated disease. Similarly, it is assumed that renal injury in IC-MPGN is mediated by complement activation triggered by immune complex deposition [9]. However, features of systemic activation of complement cascade are invariably found in patients with MPGN. For instance, a low C3 plasma level

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is noted in only 36–74% of patients with C3GN [18, 22–24] and in 15–84% of DDD patients [18, 22–24]. In IC-MPGN patients, C3 levels are low in 46–76% of cases [18, 24]. This is probably related to the fact that assays of circulating components of CAP do not necessarily reflect activation of complement within the renal tissue. Thus, normal complement component levels do not exclude the diagnosis of C3G and IC-MPGN. Interestingly, a low C4 plasm level (a marker of classical pathway activation) is present in a minority of patients with IC-MPGN (2% [18]) and the majority (70% [24]) of these patients have normal C4 and low C3, and thus features of alternative pathway activation rather than classical pathway activation. This is in sharp contrast to secondary forms of IC-MPGN (lupus and cryoglobulinemia-associated nephritis) that are characterized by decreased C4 serum levels.

Another activation product of the complement pathway, soluble C5b-9 (a marker of the terminal complement pathway), has been assessed in patients with MPGN, especially since the availability of the C5 blocker, eculizumab. In a large series of 127 cases of C3G [19], soluble C5b-9 levels were elevated in 60% of patients. However, the clinical relevance of this marker, particularly in the prediction of a clinical response to C5 blockade, remains uncertain (see infra).

The incidence of complement gene novel or rare variants is relatively low in patients with MPGN [18, 20, 22, 24], 16% in IC-MPGN, 16–33% in DDD, and 12–25% in C3GN, especially if compared to the incidence of such variants in another complement-mediated renal disease, hemolytic uremic syndrome (40–70%) [32]. The most frequently reported variants in MPGN patients are in the CFH gene (19–17%). Some of these variants lead to a total absence or a decrease in CFH plasma level while others are believed to affect the regulatory function of the protein (cluster of variants in the SCR1-3 mediating the interaction of CFH with C3b) [18, 20, 24]. Variants in the FI (0–6%), C3 (0–8%), factor B (0–2%), and MCP (0–2%) and thrombomodulin (0–1%) coding gens have been more rarely reported in IC-MPGN and C3G patients [18, 20, 22, 24]. The pathogenicity and thus clinical relevance have not been documented for the majority of these detected variants A peculiar type of C3G, highly prevalent in the Chypriote population, has been linked to internal duplication of the gene coding for complement factor H-related protein 5 (CFHR-5) leading to a decreased binding of the mutant protein to C3b [33].

In contrast, autoantibodies that interfere with the regulation of the CAP are frequently detected in C3G and IC-MPGN patients. The most documented type of autoantibodies is the C3Nef, which stabilizes the alternative C3 convertase and thus amplifies the activation of the CAP. It is present in 78–86% of DDD patients, 38–45% C3GN, and 40–53% of IC-MPGN [18, 24]. The more recently characterized C5 nephritic factor (C5Nef) [19], an autoantibody that stabilizes the C5 convertase, is present in 49% of C3G patients. C5Nef is more frequently associated with C3GN than DDD (88% vs. 33% [19]) and its presence correlates with the level of soluble C5b-9. Other types of autoantibodies have been reported in MPGN (mostly C3G) patients: anti-CFH antibodies (7–12% of patients [19, 20]), anti-C3 antibodies (2–3% [19, 34]), and anti-Factor B antibodies (2–3% [19, 34]).

Thus, MPGN appears to be related to an acquired rather than constitutional dysregulation of the complement system (mostly the CAP). However, autoantibodies detected in these patients interfere with the CAP regulation *in vitro* but their clinical relevance is still debated. In addition, the presence of autoantibodies that target the CAP in patients with IC-MPGN suggests that these nephropathies are driven not only by an activation of the classical complement pathway (triggered by immune complexes) but also by a dysregulation of the CAP.

Monoclonal Gammopathy

Several studies have outlined an association between monoclonal gammopathy and C3GN [35–37]. In the largest series of 201 patients with C3G, 29% had monoclonal gammopathy (excluding cryoglobulinemia). As expected, the prevalence of monoclonal gammopathy in patients with C3G increases with age: 36%, 59%, and 94% for the age ranges of 50–59, 60–69, and 70–79 years, respectively [37]. Even though this study may carry a recruitment bias, the association between C3GN and monoclonal gammopathy is increasingly recognized. However, there is to date no definite proof that monoclonal gammopathy per se interferes with complement dysregulation and hence is involved in the pathogenesis of the disease. Patients with monoclonal-associated C3GN have features of CAP activation (low C3 plasma level in 44% of patients) but also carry polyclonal autoantibodies interfering with the CAP regulation: C3Nef in 7% of cases (vs. 45% in all C3GN), anti-FH antibodies in 17% of cases (vs. 11%), and even anticomplement factor I and anticomplement receptor 1 antibodies [38]. In the majority of tested cases (77%) [38], these autoantibodies do not share heavy and light chain characteristics with the monoclonal gammopathy. Thus direct proof of a link between monoclonal gammopathy and C3GN is still lacking. The induction of the remission of C3GN with chemotherapy is only indirect evidence with potential bias [37].

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Toward a Global Approach for C3G and IC-MPGN

A global approach that takes into account several clinical and biological parameters is probably the most appropriate for C3G and IC-MPGN. Such approach has been recently developed by Iatropoulos and colleagues [24] using the Italian registry of C3G and IC-MPGN. Their study aimed to classify patients based on 24 variables: clinical (gender, age, triggering event at onset, familiarity for nephropathy), biological (hematuria, proteinuria, renal impairment), pathological (degree of renal inflammation and fibrosis, type and intensity of immune deposits), and those related to complement work-up (markers of complement activation, presence of complement gene variants). They identified four clusters of patients each including patients with similar presentation and renal outcome. Patients with C3G and IC-MPGN were distributed across the four subtypes. One cluster had a worse renal outcome as compared to the other clusters (renal survival at 10-year follow-up of 55% versus 85–90%). This cluster was characterized by (i) a low frequency of decreased C3 level, increased C5b-9 levels, complement genes variants, and inflammatory changes in the kidney and (ii) marked renal fibrotic changes. However, this difference in terms of renal survival may be related mainly to the intensity of fibrosis in the kidney and the absence of renal inflammatory changes that could be amended by treatment with steroids and immunosuppressors. Nevertheless, such an elegant global approach may be the key for the design of targeted individualized treatment of C3G and IC-MPGN.

Treatment of C3G and IC-MPGN

There is to date no specific treatment for C3G and IC-MPGN as no available commercialized drug targets the initial and main driver of the disease, C3 and IC deposits. The currently used drugs aim mostly to control the renal inflammation (crescents, mesangial/endocapillary proliferation) that may arise in some patients. In addition, the clinical boundaries between C3G and IC-MPGN are unclear and thus it is unclear whether treatments of these two types of MPGN should differ. Finally, there is to date no large prospective controlled trials assessing treatments options in C3G and IC-MPGN. One can only rely on open-label small prospective studies or retrospective series (Table 30.1).

The most assessed treatment in MPGN patients (mostly C3G) is mycophenolate mofetil (MMF) [39, 40], with two published series. The first, from Spain, was retrospective and multicentric. It included 60 patients with C3G with a median age of 27 years. Median serum creatinine (SCr) was 1.4 mg/dl, median estimated glomerular filtration rate (eGFR) was 66 ml/min/1.73 m^2, median proteinuria was 3.8 g/24 h, and 52% of patients had a nephrotic syndrome at baseline. The patients were divided into three groups:

a) 22 patients received MMF and steroids. The median initial dose of MMF was 1 g/day and the median treatment duration was 18 months.
b) 18 patients received immunosuppressors other than MMF: steroids alone ($n = 11$), steroids, and cyclophosphamide ($n = 7$).
c) 20 patients received no immunosuppressors.

All patients were treated with conventional antihypertensive and antiproteinuric drugs. The median follow-up was 47 months. Partial or complete clinical remission was achieved in 86% of patients treated with MMF and steroids, 50% of patients were treated with the other immunosuppressors and 25% of patients with no specific treatment ($P = 0.018$). A doubling of SCr occurred in 0%, 39%, and 35% of patients in the three groups, respectively ($P = 0.002$). The percentages of patients reaching ESRD (16-month follow-up) were 0%, 16%, and 35% in the three groups respectively ($P = 0.08$). Finally, six (27%) patients treated with MMF + Cs showed a proteinuria relapse after MMF dose tapering. This study, the first to suggest the efficacy of MMF and steroids in the treatment of C3G, carries several limitations. It was retrospective and included a limited number of patients. Pathological assessment of the kidney biopsies performed in included patients took into account the extent of fibrotic changes but not the inflammatory changes that are a major predictor of response to treatment and outcome. Furthermore, patients with significant renal fibrosis and limited inflammatory changes and thus a less active disease were probably more likely to not receive immunosuppressors. For instance only 20% of patients who received no immunosuppressor had a nephrotic syndrome at baseline as compared to 77% and 55% of patients treated with MMF or another immunosuppressor. Finally, the analysis of the individual cases of the 22 C3G patients treated with mycophenolate and steroids suggests that some of these patients had rapidly progressing glomerulonephritis, a subtype of MPGN highly likely to respond to an anti-inflammatory treatment.

The second study from the United States [40] was also retrospective but was based on a single registry. It included 30 patients with C3G and treated with MMF among 120 C3G patients diagnosed between 1997 and 2015. The median age of MMF-treated patients was 25 years, median SCr was 1 mg/dl, and median proteinuria/creatininuria ratio was 3.2 g/g. The median dose of mycophenolate was 2 g/day and the median time on therapy was 24 months.

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Table 30.1 Main series and prospective trials that assessed treatment options in patients with C3G and IC-MPGN.

References	Type of study	Drug assessed	Number of patients	Main results	Limitations	Level of evidence
MMF in C3G						
Rabasco et al [39]	Retrospective, national, multicentric.	Cs + MMF Other IS (Cs ± CYP)	Total: $n = 60$ Cs + MMM ($n = 22$) Other IS ($n = 18$) No IS ($n = 20$)	Partial or complete clinical remission[a] achieved in 86% of MMF + Cs patients, 50% of patients with other IS, and 25% of patients with no IS ($P = 0.018$). A doubling of SCr occurred in 0%, 39%, and 35% of patients in the three groups, respectively (0.002). The percentages of patients reaching ESRD (16 months follow-up) were 0%, 16%, and 35% in the three groups, respectively ($P = 0.08$). Six (27%) patients treated with MMF + Cs showed a proteinuria relapse after MMF dose tapering.	Retrospective and multicentric. Limited number of included patients. Patients with significant renal fibrosis and limited inflammatory changes were probably more likely to not receive IS. Some patients treated with Cs + MMF had RPGN, a subtype of MPGN highly likely to respond to an anti-inflammatory treatment.	Low
Avarese et al [40]	Retrospective, single register.	Cs + MMF Cs + various IS	Total: $n = 73$ Cs + MMF ($n = 30$) Cs alone ($n = 23$) Cs + CNI ($n = 7$) Cs + RTX ($n = 7$) Cs + CYP ($n = 6$)	67% of patients treated with MMF + Cs were classified as responders[b] to treatment as compared to 39%, 33%, 29%, and 29% of those treated with Cs alone, Cs + CYP, CNI, and RTX. Patients who responded to MMF + Cs tended to have lower initial proteinuria and higher soluble membrane attack complex levels as compared to nonresponders (not statistically significant). Fifty percent of patients who responded to eculizumab had a proteinuria relapse after treatment tapering/discontinuation.	Retrospective study. Limited number of patients in each treatment group. Patients with significant renal fibrosis and limited inflammatory changes were probably more likely to not receive IS. Comparison between responders and nonresponders to MMF (and between MMF and other IS) did not take into account the presence or absence of inflammatory changes in the kidney.	Low
MMF in IC-MPGN						
Jones et al [41]	Retrospective	Cs + MMF	Cs + MMF ($n = 5$) Compared to seven untreated patients (six with IC-MPGN and one with DDD)	In the MMF + Cs group, proteinuria decreased from 5 g/day at baseline to 1.9 g/24 h ($P = 0.003$) at 6 months, 1.96 g/24 h ($P = 0.003$) at 12 months, and 2.59 g/24 h ($P = 0.015$) at 18 months. No change in proteinuria over 18 months in occurred in the control group (MMF + Cs vs. controls, $P = 0.03$). In the MMF + Cs group, serum albumin concentration increased from 29 g/l at baseline to 36.6 g/l at 6 months, 38.2g/l at 12 months, and 37 g/l after 18 months.	Retrospective with very limited number of patients. Relatively low dose of MMF (mean dose of 1 g/day) and high dose of Cs (60 mg/day initially).	Absent

(*Continued*)

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Table 30.1 (Continued)

References	Type of study	Drug assessed	Number of patients	Main results	Limitations	Level of evidence
Eculizumab in C3G						
Le Quintrec et al [27]	Retrospective, multicentric	Eculizumab	26 patients (13 children/ adolescents) with C3G	23% of patients had a global clinical response, 23% a partial clinical response, and 54% no response[c]. Compared with those who had a partial clinical or no response, patients who had a global clinical response had lower estimated glomerular filtration rates, a more rapidly progressive course, and more extracapillary proliferation in kidney biopsy.	Retrospective design without a control group, relatively small number of cases. Inclusion of pediatric and adult cases.	Low
Bomback et al [42]	Prospective, open-label, noncontrolled, and monocentric	Eculizumab.	Six patients: three with DDD (one with a recurrence in the renal graft), three with C3GN (including two with a recurrence in the renal allograft).	After 12 months of treatment, two patients had a decrease in serum creatinine, one patient had a significant reduction in proteinuria. Three patients had no clinical response, including one with an improvement in inflammatory changes in the kidney. Changes in soluble C5b–9 serum levels paralleled the improvement in serum creatinine and proteinuria.	Noncontrolled. Very limited number of patients.	Low

C3GN, C3 glomerulonephritis; CNI, calcineurin inhibitor; Cs, corticosteroids; CYP, cyclophosphamide; DDD, dense deposits disease; IS, immunosuppressors; MMF, mycophenolate mofetil; RPGN, rapidly progressing glomerulonephritis; RTX, rituximab; SCr, serum creatinine.

[a] Complete remission was defined by eGFR of 460 ml/min/1.73 m^2 (or a return to ±15% of baseline values in those with eGFR < 60 ml/min/1.73 m^2) and proteinuria <0.5 g/24 h. Partial remission was defined by a proteinuria reduction of >50% (and a proteinuria value of o3.5 g/day in patients with nephrotic range proteinuria at baseline), plus stabilization (±25%) or improvement in renal function.

[b] Complete remission of the disease was defined by a stable or improved eGFR with decline in proteinuria/creatininuria ratio to <0.5 g/g creatinine. Partial remission was defined by stable or improved eGFR with >50% decline in proteinuria/creatinuria ratio to between 0.5 and 3.5 g/g Cr by urine protein-to-Cr ratio at last follow-up. Stable eGFR was defined as within 15% of baseline. Patients were categorized as "responders" if they had either complete or partial remission concordant with MMF treatment.

[c] Response to eculizumab was characterized as: (1) global clinical response, defined as (a) >50% decrease in serum creatinine concentration and urinary protein-creatinine ratio (UPCR) and serum albumin concentration >3 g/dl or (b) the persistence of normal serum creatinine concentration (±10%) and albumin concentration >3 g/dl and normalization of UPCR (<150 mg/g), or (2) partial clinical response, defined as (a) <50% decrease in serum creatinine concentration, albumin concentration > 3 g/dl, and >50% decrease in UPCR or (b) the persistence of normal serum creatinine concentration (±10%), albumin concentration >3 g/dl, and >50% decrease in UPCR.

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Mycophenolate mofetil was associated with steroids in 93% of cases. Twenty patients (67%) had a response to MMF and achieved partial or complete response to treatment. The median time to response was 10 months. Four out of eight patients who discontinued MMF had a proteinuria relapse. The remission rate with MMF in combination with steroids (67%) was higher than the one achieved with steroids alone (39%), steroids in combination with cyclophosphamide (33%), calcineurin inhibitor (29%), and rituximab (29%).

Mycophenolate mofetil has been assessed in a single small retrospective series of IC-MPGN patients [41]. Five patients with IC-MPGN were treated with MMF (mean dose 1.1 g/day) and high-dose steroids. At baseline, their median SCr was 1.1 mg/dl (mean creatinine clearance of 108 ml/min) and their mean proteinuria was 6 g/day. Their evolution was compared to that of seven untreated patients, six with IC-MPGN and one with DDD. In the mycophenolate and steroids group, proteinuria decreased from 5 g/day at baseline to 1.9 g/24 h ($P = 0.003$) at 6 months, 1.96 g/24 h ($P = 0.003$) at 12 months, and 2.59 g/24 h ($P = 0.015$) at 18 months. No change in proteinuria over 18 months in occurred in the control group (MMF + steroids vs. controls, $P = 0.03$). In the MMF + steroids group, serum albumin concentration increased from 29 g/l at baseline to 36.6 g/l at 6 months, 38.2 g/l at 12 months, and 37 g/l after 18 months.

In all, the level of evidence of the usefulness of mycophenate mofetil in C3G is low and absent in IC-MPGN. Nevertheless, mycophenolate associated to a variable dose of steroids is increasingly used in patients with chronic/subacute nephrotic patients with C3G and by analogy in patients with IC-MPGN.

The availability of the first complement inhibitor, the C5 blocker, eculizumab, has initially raised a lot of interest in this drug as a potential treatment for MPGN. Eculizumab has been assessed in two series of C3G patients, with very discrepant results. The largest one from France was retrospective [27], noncontrolled, and included 26 patients, of whom 13 were children or adolescents. At the initiation of eculizumab therapy, 42% patients had chronic kidney disease, 73% had nephrotic syndrome, 27% had rapidly progressive disease, and 12% required dialysis. Median time from diagnosis to eculizumab treatment initiation was 16 months. The eculizumab regimen was similar to the one used in atypical hemolytic uremic syndrome (HUS) [32]: 900 mg intravenously per week for 4 weeks and then 1200 mg intravenously on week 5 and every other week afterward. At eculizumab treatment initiation, median SCr concentration was 0.6 mg/dl in children/adolescents and 2.3 mg/dl in adults, corresponding to a median eGFRs of 110 and 28 ml/min/1.73 m^2, respectively. Twenty-three percent of patients had a global clinical response, 23% had a partial clinical response; and 54% had no response. Compared with those who had a partial clinical or no response, patients who had a global clinical response had lower eGFRs, a more rapidly progressive course, and more extracapillary proliferation on kidney biopsy. Age, extent of renal fibrosis, frequency of nephrotic syndrome, low serum C3 and C3Nef, and elevated soluble C5b-9 concentrations or complement gene variants did not differ between responders and nonresponders.

The second smaller series from the United States [42] included six patients: three patients with DDD (one patient had a recurrence of the disease in the renal allograft) and three patients with C3GN (two patients had a recurrence of the disease in the renal allograft). The eculizumab regimen was similar to the one used in atypical HUS. After 12 months of treatment, two patients had a decrease in SCr and one patient had a significant reduction in proteinuria. Three patients had no clinical response, including one with an improvement in inflammatory changes in the kidney. Changes in soluble C5b-9 serum levels paralleled the improvement in SCr and proteinuria. No series or trials have to date assessed the use of eculizumab in IC-MPGN but one case report has suggested some efficacy of the drug [43].

No definitive conclusions can be drawn from this series regarding the use of eculizumab in C3G and IC-MPGN. Nevertheless, eculizumab does not appear to be the specific long-awaited treatment for MPGN. The lack of a significant impact of eculiuzmab on the course of MPGN may be due at least in part to the fact that these nephropathies have two aspects. All patients with MPGN display immune deposits (C3 with or without immunoglobulins) and a variable minority of patients have additional features of glomerular inflammation (mesangial and endocapillary proliferation, crescents) that probably depend on the release of C5a and/or C5b. Eculizumab most probably treats only one aspect of the disease (inflammatory changes) with no or very limited impact on C3 and immunoglobulins deposits. Eculizumab may be a potent inflammatory drug in patients with inflammatory forms of C3G, as suggested by the retrospective French series [27] where only patients with crescentic and rapidly progressing forms of C3G had a significant and cost-effective response to eculizumab.

Conclusion

Experimental and clinical studies have transformed the perspective in the management of C3G and IC-MPGN. It remains unknown, however, whether the distinction between these two types of nephropathies within the group of MPGN is clinically relevant. There is to date no specific

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treatment of C3G and IC-MPGN, which directly targets the initial driver of the disease, C3, and possibly immunoglobulins deposition. Nevertheless, several complement modulators that inhibit the activation of the alternative C3 convertase are currently being developed [44] and specific treatment for C3G and IC-MPGN may be within our reach.

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Part 5

Chronic Kidney Disease and Complications

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Cardiovascular Disease and CKD

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Introduction

Chronic kidney disease (CKD) is an important risk factor for cardiovascular morbidity and mortality. Cardiovascular disease (CVD) is the name for a group of disorders of the heart and blood vessels, including hypertension, coronary heart disease, cerebrovascular disease, peripheral vascular disease, and heart failure. Reduced kidney function and raised albuminuria are both independent risk factors for CVD [1, 2]. By 2013, cardiovascular death attributable to reduced glomerular filtration rate (GFR) outnumbered end-stage renal disease (ESRD) death in both developed and developing countries [3].

The increased risk of CVD in CKD patients is partly attributed to high prevalence of comorbidities, such as hypertension, diabetes mellitus, dyslipidemia, and obesity. There is not high-quality evidence for the selection of treatment of CKD patients to prevent CVD. Many randomized controlled trials (RCTs) have investigated treatment of disease associated with CVD, but CKD patients are often excluded from these RCTs. It is not clear whether the results of clinical studies in patients with non-CKD may be extrapolated to CKD patients. The increased risk of CVD in CKD patients is not fully explained by the traditional risk factors. The nontraditional risk factors derived from CKD itself may also be important. Systematic reviews and meta-analysis of post hoc analysis of the CKD subgroup and observational studies are performed to produce evidence for CKD patients.

This chapter examines the evidence for the epidemiology, pathophysiology, diagnosis, prognosis, and management of CVD in people with CKD (Table 31.1). We excluded kidney transplant or dialysis patients that will be covered in other places (Parts 6, 7, and 9).

Definition

CVD is a name for the group of disorders of the heart and blood vessels. This includes hypertension, coronary heart disease, cerebrovascular disease, peripheral vascular disease, and heart failure. CVD may progress over years and CKD patients may develop cardiomyopathy, valve dysfunction, and arrhythmia (e.g. atrial fibrillation) or sudden cardiac death.

Epidemiology

In a cohort of 3033 patients with CKD stages 3–4 (mean age 66.8 years, 65% men), the prevalence of CVD was examined [19]. CVD was divided into atherosclerotic (coronary artery disease [CAD], peripheral artery disease, and stroke) and nonatherosclerotic (heart failure, arrhythmia, and valvular heart disease). In age groups <65, 65–74, 75–84, and ≥85 years the prevalence of atherosclerotic CVD was 18.7%, 35.5%, 42.9%, and 37.8%, respectively, and that of nonatherosclerotic CVD, 14.9%, 28.4%, 38.1%, and 56.4%, respectively. The prevalence of both atherosclerotic and nonatherosclerotic CVD increased with older age.

The prevalence of heart failure in CKD patients is high and it was similar among studies. In the European Heart Failure Pilot Survey, comorbidities of a total of 3226 outpatients with chronic heart failure were examined; the highest comorbidity was CKD (41%) [20]. In the Swedish Heart Failure Registry and the Asian Sudden Cardiac Death in Heart Failure registry, prevalence of CKD in patients with heart failure was 43.9% and 45.4%, respectively [21, 22].

In the Atherosclerosis Risk in Communities (ARIC) study, 10 328 subjects were followed for median of 10.1 years

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Table 31.1 Treatment for cardiovascular disease (CVD) with chronic kidney disease (CKD).

Treatment	Recommendation	Certainty of evidence	Strength of recommendation
Blood pressure lowering	We suggest blood pressure lowering to prevent cardiovascular events for patients with CKD. There was little evidence to support the preferential choice of particular drug classes for the prevention of cardiovascular events in CKD. The specific target blood pressure is not confirmed for patients with CKD.	High (cardiovascular events)	Moderate [4–6]
Statin therapy	We suggest statins to decrease cardiovascular mortality and events in early stages of CKD.	High (cardiovascular mortality in CKD stages 3–5) Moderate (major cardiovascular events in CKD stages 3–5)	Weak [7–9]
Antiplatelet agents	We suggest antiplatelet agents can be used to lower risk of myocardial infarction. Patients with CKD (any stage) may reasonably choose not to receive antiplatelet agents based on the very low certainty that treatment makes any difference to mortality and stroke, and there is increased risk of major or minor bleeding.	Low	Weak [10]
Glycemic control	We suggest sodium glucose co-transporter-2 (SGLT2) inhibitors may be used in patients with diabetes and CKD to lower kidney failure and cardiovascular events risk. Patients with diabetes and CKD may reasonably choose not to receive SGLT2 inhibitors based on the very low certainty that the treatment makes any difference on mortality and may increase genital infections and creatinine.	Moderate (kidney failure and cardiovascular events)	Moderate [11, 12]
Anticoagulants	We suggest warfarin to prevent mortality, ischemic stroke, or thromboembolism in patients with atrial fibrillation and CKD. We suggest direct oral anticoagulants to prevent stroke and systemic embolic events without increasing risk of major bleeding events among atrial fibrillation patients with CKD compared to warfarin.	Low (warfarin) Moderate (direct oral anticoagulants, stroke, and systemic embolic events) Low (direct oral anticoagulants, major bleeding events)	Moderate [13, 14]
Coronary revascularization	We suggest percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) for coronary artery disease with CKD. We suggest drug-eluting stents compared to bare-metal stents for PCI. PCI is associated with lower early (30 days) mortality, but the need for repeat revascularization was significantly higher compared to CABG.	Low	Moderate [15, 16]
Dietary restrictions	We suggest that reduced dietary salt may be used to reduce blood pressure. Long-term effect of reduced dietary salt on cardiovascular events is not confirmed.	Very low	Weak [17, 18]

and incident atrial fibrillation cases was identified [23]. Incidence of atrial fibrillation by estimated glomerular filtration rate (eGFR) ≥90, 60–89, 30–59, and 15–29 ml/min/1.73 m^2 was 6.4, 5.6, 9.5, and 36.2 per 1000 person-years, respectively, and by urinary albumin to creatinine ratio <30, 30–299, and ≥300 mg/g was 5.8, 14.6, and 26.3 per 1000 person-years, respectively. The reduced kidney function and higher albuminuria were associated with higher incident atrial fibrillation.

Pathophysiology

CVD is the primary cause of morbidity and premature mortality in CKD. There may be several reasons for the increased risk of CVD in CKD patients [24]. CKD patients have increased prevalence of traditional and nontraditional risk factors for CVD. CKD itself is an independent risk factor for CVD. CVD and many risk factors for CVD are also risk factors for CKD. CKD and CVD interact to

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contribute to the progression of both diseases, resulting in the cardiovascular and kidney disease progression cycle.

Systemic vascular remodeling may cause CVD. The risk of stroke and myocardial infarction increased with elevating blood pressure in a large cohort with or without CKD [25]. The subjects with CKD had increased risk of CVD with higher blood pressure compared to subjects without CKD. The association of blood pressure and CVD may be increased in CKD patients.

The long-term pressure and volume overload in CKD causes concentric left ventricular hypertrophy and left ventricular dilation [26]. Cardiomyopathy progression will cause diastolic and systolic dysfunction. In a cohort of patients with CKD stages 3–4, 30% had left ventricular hypertrophy [27]. The left ventricular mass increase was confirmed in 36% of a CKD cohort with creatinine clearance between 25 and 75 ml/min/1.73 m^2 [28]. After 1 year, left ventricular mass increased in 25% of the subjects. The independent risk factors for left ventricular growth were decrease in hemoglobin level and increase in systolic blood pressure. Anemia may also cause left ventricular hypertrophy.

In a cross-sectional study of 118 hemodialysis patients, systolic blood pressure, pulse pressure, extra-coronary atherosclerosis, and vascular calcification correlated with left ventricular mass [29]. In a cohort of patients with CKD stage 5D, the prevalence of left ventricular hypertrophy was 16.4% [30]. The left ventricular hypertrophy was associated with higher mortality during the follow-up period of 2 years. During the 10-year follow-up of 123 patients undergoing hemodialysis, 16 died of sudden cardiac death [31]. The worsening of left ventricular mass index (LVMI) was highly associated with the sudden cardiac death.

Dyslipidemia of CKD patients is characterized by dysregulated high-density lipoprotein cholesterol (HDL-C) and triglyceride-rich lipoprotein metabolism [32]. Plasma triglyceride concentration is frequently elevated in patients with CKD. These abnormalities in CKD patients may cause dysregulation of lipid metabolism, which contributes to atherogenic change and increases the risk of CVD.

Abdominal obesity is known to be associated with increased risk of CVD. In a prospective cohort of 537 subjects with ESRD, waist circumference was associated with all-cause and cardiovascular mortality [33]. Adipose tissue secretes a number of adipokines and cytokines and works as an important organ [34]. The complex role of adipose tissue as not only an energy storage organ but its interaction with the systemic vascular system is not fully known.

Atherosclerotic and arteriosclerosis change may be the cause of CVD in CKD patients. Many studies report the existence of subclinical atherosclerosis in CKD patients. Even among asymptomatic subjects aged 23–43 years, subjects with albuminuria had significantly higher intima-media thickness than those without albuminuria [35]. Aortic stiffness measured by aortic, brachial artery, and femoral pulse wave velocity was independently associated with cardiovascular mortality in ESRD patients [36].

In 117 autopsy subjects with CAD, the association between coronary artery calcification (CAC) and CKD was evaluated [37]. CAC was present in the intimal plaque of both nonkidney and kidney patients. Age, smoking, diabetes, calcium phosphorus product, inflammation, and kidney function were associated with intimal calcification. In a study of 1541 CKD patients, the association between CAC and cardiovascular events during an average follow-up of 5.9 years was examined [38]. CAC was independently and significantly related to risk of CVD, myocardial infarction, and heart failure in CKD patients.

Endothelial dysfunction has been proposed to be an early phase of the atherosclerotic process [39]. It is characterized by a shift in the actions of the endothelium toward reduced vasodilation, a proinflammatory state, and prothrombotic properties. Reduced nitric oxide generation, oxidative excess, and reduced production of hyperpolarizing factor are the mechanisms in endothelial dysfunction. Upregulated adhesion molecules, generation of chemokines, and production of plasminogen activator inhibitor-1 participate in the inflammatory response. Vasoactive peptides, an endogenous nitric oxide inhibitor, and dyslipidemia may also interact to contribute to these mechanisms.

In addition to traditional risk factors, many nontraditional risk factors that are directly and indirectly associated with CKD contribute to CVD pathophysiology. In a meta-analysis of 21 cohort studies, the association between routinely collected risk factors and CVD was examined [40]. Left ventricular hypertrophy, serum albumin, phosphate, urate, and hemoglobin were associated with the increased risk of CVD.

Low-grade inflammation is recognized as a common pathway of CKD and CVD [41]. Increased inflammation markers, such as high-sensitivity C-reactive protein (hs-CRP), white blood cell count, and fibrinogen, were associated with peripheral artery disease in CKD patients [42]. After a median follow-up of 6.3 years, the same inflammation markers were associated with increased risk of incident peripheral artery disease [43]. Higher levels of hs-CRP and interleukin-6 (IL6) were also associated with higher risk of sudden cardiac death in a cohort undergoing hemodialysis or peritoneal dialysis [44].

Cardiac and kidney diseases interact in both acute and chronic settings [45]. The bi-directional links between cardiac and kidney function are perceived as cardio-renal syndrome. The interaction includes activation of the renin-angiotensin aldosterone system (RAAS), activation

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of the sympathetic nervous system, uremic toxins, malnutrition, bone and mineral disorder, and oxidative stress [46–52]. Acute kidney injury (AKI) was associated with increased risk of heart failure, acute myocardial infarction, and stroke [53]. Anemia was associated with increased risk of stroke and coronary heart disease [54, 55]. The mechanism by which cardio-renal syndrome advances CVD has not been fully elucidated.

Serum potassium level may also be an important risk factor for CVD in CKD patients. A cohort of nondialysis CKD patients was followed for a median of 2.8 years [56]. Mortality, major adverse cardiovascular events, and hospitalization were significantly higher among those with both low and high serum potassium levels. A predialysis serum potassium of 4.6–5.3 mEq/l was associated with the greatest survival in a cohort of 81 013 maintenance hemodialysis patients followed for 3 years [57]. In a retrospective study of 228 hemodialysis patient deaths, 80 patients met the criteria of sudden death [58]. Patients with sudden death had high prevalence of congestive heart failure (CHF) and CAD (CHF or CAD were present in 71%), and 25% had a serum potassium level less than 4.0 mEq/l. In CKD patients with CAD, hyperkalemia (serum $K > 5.0$ mEq/l) occurred more frequently than hypokalemia (serum $K < 3.5$ mEq/l) (16.7% vs. 3%), and hyperkalemia was associated with risk of sudden cardiac death [59]. Potassium works as a critical factor to maintain cardiovascular health [60]. CKD patients may have serum potassium abnormalities, which includes both hypokalemia and hyperkalemia. The factors associated with abnormal potassium levels are declined kidney function, endogenous, and exogenous catecholamine activity, activation of RAAS and anti-RAAS inhibitor agent and RAAS blocker agents, and potassium wasting diuretics.

Diagnostic Tests

CVD is highly prevalent in CKD patients. Early detection of CVD in CKD patients may lead to modification of risk factors and pharmacological intervention. However, diagnosis of CVD in CKD patients may be difficult. The accuracy of diagnostic tests is often reduced. The symptoms of CVD may be difficult to distinguish from volume overload or uremia in CKD patients. There are several systematic reviews for the diagnosis of CVD in CKD patients [61–65]. The diagnostic tests to evaluate CVD in CKD patients are outlined in Table 31.2.

Biochemical Abnormalities

Clinical practice guidelines and review of diagnosis of CVD in CKD recommend biomarkers including lipid profile, hs-CRP, B-type natriuretic peptides (BNP), and troponins.

Lipid Profile

It is recommended that CKD patients be evaluated with a lipid profile (total cholesterol, low-density lipoprotein cholesterol [LDL-C], high-density lipoprotein cholesterol [HDL-C], triglycerides, nonhigh-density lipoprotein cholesterol [non-HDL-C]) [66, 67]. The lipid profile should be measured in the fasting state. Fasting mainly affects triglycerides level and does not affect HDL-C level. The appropriate frequency of the measurement of lipid profile is not known. Some guidelines recommend lipid-lowering therapy with treatment target of LDL-C < 70 mg/dl or non-HDL-C < 100 mg/dl. However, the Kidney Disease: Improving Global Outcomes (KDIGO) Guideline for Lipid Management does not recommend the treat-to-target strategy due to the lack of its benefit in any clinical trial [66].

Inflammation

Inflammation markers such as hs-CRP, IL-6, tumor necrosis factor (TNF), and white blood cell counts are found to be associated with increased risk of CVD events and mortality. However, there are no thresholds or criteria to diagnose the increased risk of CVD for those markers.

The frequency of sudden cardiac death and its association with inflammation and other risk factors were examined among 1041 incident dialysis patients from the CHOICE (Choices for Healthy Outcomes In Caring for ESRD) cohort over a median 2.5 years of follow-up [68]. Of all subjects, 22% of all mortality in this cohort was due to sudden cardiac death. The highest tertiles of hs-CRP and of IL-6 were each associated with twice the risk of sudden cardiac death compared to their lowest tertiles when adjusted for demographics, comorbidities, and laboratory factors. Among 543 patients with stage 5 CKD, IL-6, white blood cell counts, and TNF independently predicted all-cause mortality during the follow-up of 28 months [69].

B-Type Natriuretic Peptides

Brain natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) are used for diagnosis and prognosis of heart failure. NT-proBNP has a longer half-life than BNP and it may be less sensitive to acute change. The plasma BNP and NT-proBNP levels are higher in CKD patients [70–72]. The BNP level is influenced by kidney function, anemia, obesity, and heart failure.

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Table 31.2 Summary of diagnostic tests in cardiovascular disease (CVD) with chronic kidney disease (CKD).

Test	What does it measure?	Comments
Biochemical		
Lipid profile	• Includes total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, non-HDL-cholesterol, triglycerides	• The current guideline recommend to measure lipid profile at first presentation with CKD • No further measurement is required unless the results would change management
High-sensitivity C-reactive protein	• Measures circulating high-sensitivity C-reactive protein (hs-CRP) • Reflects increased inflammation status, which is associated with increased risk of CVD events and mortality	• No thresholds of change is specified in CKD patients
B-type natriuretic peptides	• Measures circulating B-type natriuretic peptides (BNP) or N-terminal-pro-BNP (NT-pro-BNP) concentration • Commonly used with patients with symptoms of heart failure • Association with abnormal echocardiographic findings	• CKD patients have elevated BNP and NT-pro-BNP levels • No thresholds of change is specified in CKD patients
Troponins	• Measures circulating cardiac troponin T (cTnT) or cardiac troponin I (cTnI) • Association with cardiac injury such as myocardial infarction	• Patients with kidney dysfunction have elevated troponins levels • No thresholds of change is specified in CKD patients
Electrocardiogram		
12-lead electrocardiogram	• Measures baseline rhythm, presence of Q waves, chamber enlargement, left ventricular hypertrophy	• Exercise stress electrocardiogram may be performed
24 h Holter monitor	• Records all beats over 24-h period • Identifies ST segment shifts or asymptomatic arrhythmias	
Imaging		
Resting echocardiography	• Evaluates diastolic and systolic function and valve disease	• Noninvasive
Exercise stress echocardiography	• Evaluates exercise-related functional status • Identifies fixed and reversible ischemia	• No radiation • Appropriate for low risk CVD and severe CKD stages
Exercise stress nuclear scintigraphy or Pharmacologic stress imaging	• Evaluates exercise-related functional status • Identifies fixed and reversible ischemia	• Radiation or drug usage • Requires specific scanner, not available in many clinical settings
Left ventricular hypertrophy or left ventricular dysfunction	• Measures left ventricular mass index (LVMI) or left ventricular function by echocardiography • Association with CVD mortality	• Noninvasive • Patients with advanced CKD stages have increased LVMI • Uncertain diagnostic utility in CKD
Carotid intima-media thickness	• Measures the thickness of the intima-media of the artery on an ultrasound image • Association with cardiovascular events	• Noninvasive • Uncertain diagnostic utility in CKD

(*Continued*)

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Table 31.2 (Continued)

Test	What does it measure?	Comments
Cardiac computed tomographic angiography	• Generates calcium score, which can evaluate degree of lumen stenosis if calcification is not severe	• Appropriate for the evaluation of chest pain with uninterpretable stress test • Not appropriate for established coronary artery disease or ESRD
Coronary artery calcification	• Measures coronary artery calcification (CAC) by computed tomography • Association with the risk of CVD	• Radiation • CKD patients have higher CAC scores • Uncertain diagnostic utility in CKD • Not recommended in routine clinical care
Coronary angiography	• Detects blockages in the coronary arteries	• Uses contrast dye containing iodinine, which may cause contrast-associated AKI • Radiation
Single-photon emission computed tomography (SPECT) or positron emission tomography (PET)	• Measures myocardial function, left ventricular volume, and ejection fraction	• Noninvasive • Requires specific scanner, not available in many clinical settings
Cardiac magnetic resonance or cardiac MRI	• Measures left ventricular mass, volume, and ejection fraction	• Noninvasive

Troponin

Troponins (troponin I and troponin T) are used as a marker of myocardium damage [73]. Myocardial infarction is diagnosed a rise and/or fall from the norm of cardiac biomarkers, preferably cardiac troponin (cTn). The diagnosis of myocardial infarction in CKD patients may be difficult because patients with kidney dysfunction can have an increased troponin level, so the diagnosis of myocardial infarction may be difficult [74]. The cTn cutoff levels in patients with kidney dysfunction were significantly higher compared to those in patients with normal kidney function. The optimal cutoff levels to separate AMI from other conditions underlying acute chest pain in the emergency department in patients with kidney dysfunction were close to the elevated baseline levels above the 99th percentile for the 3 s-cTn assays (1.0 times the 99th percentile for Abbott–Architect s-cTnI, 1.2 times the 99th percentile for Siemens Ultra s-cTnI, and 0.9 times the 99th percentile for Beckman–Coulter Accu s-cTnI) and substantially higher for most hs-cTn assays (2.1 times the 99th percentile for Roche hs-cTnT, 1.1 times the 99th percentile for Abbott–Architect hs-cTnI, 3.6 times the 99th percentile for Siemens hs-cTnI, and 2.8 times the 99th percentile for Beckman–Coulter hs-cTnI) [75]. The higher cTnT and cTnI levels in patients with CKD stage 5D show a two to fivefold increase in mortality [76].

Electrocardiogram

The electrocardiogram (ECG) evaluates baseline rhythm, presence of Q-waves, chamber enlargements, and left ventricular hypertrophy. The findings of ECG in CKD patients in acute myocardial infarction may be different from those without CKD [77]. In a study of 1876 elderly myocardial infarction patients, the patients with CKD had lower peak creatinine kinase-MB fraction (CK-MB) level and ST-elevated myocardial infarction was less common compared to those without CKD [78].

Imaging

Echocardiography

Echocardiography is useful for the diagnosis of clinical and subclinical cardiac dysfunction, for the prediction of cardiovascular risk, and in the orientation and follow-up of treatment strategies in CKD patients [79, 80]. Echocardiogram may be repeated for a patient periodically and with changes in symptoms, new clinical event, or a treatment likely to affect cardiac function. Among 567 subjects with CKD and without history of CVD, LVMI evaluated by echocardiogram was an independent risk factor for incident heart failure during median follow-up period of 6.6 years [81]. The delay in or absence of renal replacement therapy results in dyspnea due to fluid overload even if the patient's heart is structurally normal. The new functional classification system of heart failure in patients with CKD stage 5 are proposed to exclude patients with volume overload and a normal heart [82]. The classification is based on patient-reported symptoms and standardized echocardiographic evidence of structural and functional heart abnormalities. When this system was applied to 654 patients who

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began chronic hemodialysis, 87% of patients had one or more of echocardiographic criteria of heart failure [83]. During a median of 2.4 years, both left and right ventricular systolic dysfunction were independent risk factors for mortality.

Coronary Angiography

Coronary angiography uses contrast dye and X-ray to diagnose CAD. CKD patients need special consideration due to potential contrast-associated AKI [84]. The efficacy of prophylactic intravenous hydration for prevention of contrast-associated AKI differs among studies [85, 86]. The type of contrast media may have different effect on kidney function. The use of iso-molar and low-osmolar contrast media in patients with CKD stage 3–5 showed nonsignificant difference in incidence of contrast-associated AKI in a meta-analysis of randomized trials [87].

Computed Tomography

CAC can be measured by computed tomography. CAC was independently associated with the risk of CVD and mortality in CKD patients [40]. However, the clinical utility of CAC is unknown due to lack of enough data in CKD patients. In a cohort study of 3218 CKD subjects followed for 12.5 years, elevated BNP, NT-proBNP, and cTnT and left ventricular hypertrophy were associated with cardiovascular events or death [88]. CAC did not improve risk prediction when added to traditional risk factors in this study.

Myocardial Perfusion Imaging

Myocardial perfusion imaging is nuclear imaging of the function of myocardium. Single-photon emission computed tomography (SPECT) or positron emission tomography (PET) can be performed [80]. In a prospective cohort study with 299 CKD patients who underwent SPECT, the scores calculated as the difference between stress and rest images were associated with high major cardiovascular or kidney events [89].

Cardiac Magnetic Resonance

Cardiac magnetic resonance or cardiac magnetic resonance imaging (MRI) is noninvasive imaging that does not use contrast administration or radiation. In 72 patients with CKD stage 5D, ECG and SPECT had low sensitivity in detecting myocardial infarction [90]. Cardiac MRI with myocardial delayed enhancement identified unrecognized myocardial infarction.

Prognosis

CKD patients are known to have high risk of cardiovascular morbidity and mortality. Several studies examined the activities of daily living, kidney disease progression, or mortality after cardiovascular events in CKD patients.

A total 3352 CKD patients with CAD diagnosed with angiography were followed for 2 years [91]. At baseline, 31.3% of patients with eGFR ≥90 ml/min/1.73 m^2 had one-vessel, 34.3% had two-vessel, and 33.9% had three-vessel CAD. In patients with eGFR <30 ml/min/1.73 m^2 or on dialysis, the proportion of patients with one-vessel CAD was 16.8% and 54.5% had three-vessel CAD. The significant risk factors for 2-year all-cause mortality were lower eGFR, current smoking, left ventricular ejection fraction, diabetes mellitus, age, and peripheral artery disease. Peripheral artery disease diagnosed with ankle-brachial index <0.9 was also an independent predictor of major adverse cardiovascular events in 3131 CKD patients hospitalized for CVD [92].

Management

As CKD patients are at high risk of cardiovascular morbidity and mortality, the management of both traditional and nontraditional risk factors is of importance [93, 94]. In randomized trials of treatment of traditional risk factors, CKD patients are often excluded. The robust evidence for the management of CKD patients is limited (Tables 31.3–31.8). The control of blood pressure may have some benefits in CKD patients, but the target blood pressure for the prevention of CVD is not confirmed. Lipid-lowering therapy reduced cardiovascular mortality in CKD patients without dialysis or kidney transplant. The risk reduction of CVD by antiplatelet therapy was not confirmed. Some classes of blood glucose agents may reduce cardiovascular events, but there is a lack adequate high-quality studies. Lifestyle modification may be recommended based on observational studies, but few studies have confirmed the effect on CVD in CKD patients. Anticoagulants therapy for patients with atrial fibrillation reduced the risk of thromboembolism and stroke. Coronary revascularization for patients with CAD was evaluated and the short-term and long-term outcome may differ according to the treatment.

Patients with CKD and acute CAD or stroke are less likely to receive evidence-based medicine [95–98]. The reason for this attitude toward CKD patients may be due to atypical symptoms and difficulty in the diagnosis of CVD in CKD patients, or concerns of AKI after diagnostic method or treatment. Meta-analysis of 10 observational and randomized clinical studies examined the association between early invasive approach and all-cause mortality in CKD patients [99]. Early invasive approach was associated with lower risk of mortality.

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Table 31.3 Summary of findings: blood pressure control.

Outcomes	No. of participants (no. of studies)	Absolute number of patients affected per 1 000 patients treated for 1 year (95% CI)	Relative risk (95% CI)	Certainty of the evidence (GRADE)	Conclusion
Angiotensin converting enzyme inhibitors versus placebo					
Major cardiovascular events	10 044 (13)	–	HR 0.81 (0.73–0.89)	High	Angiotensin converting enzyme inhibitors may reduce major cardiovascular events
Calcium channel blockers versus placebo					
Major cardiovascular events	1 855 (6)	–	HR 0.74 (0.53–1.03)	Moderate	Calcium antagonists therapy may reduce major cardiovascular events
More intensive blood pressure lowering versus less intensive blood pressure lowering					
Mortality	15 924 (3)	–	OR 0.86 (0.75–0.97)	High	Intensive blood pressure lowering may reduce mortality
Cardiovascular mortality	2 646 (4)	–	HR 0.57 (0.31–1.02)	Moderate	It is uncertain whether intensive blood pressure lowering may reduce cardiovascular death
Composite cardiovascular outcome	2 646 (4)	–	HR 0.81 (0.63–1.05)	Moderate	It is uncertain whether intensive blood pressure lowering may reduce cardiovascular events
Acute kidney failure	2 646 (4)	–	HR 1.46 (1.10–1.95)	Moderate	Intensive blood pressure lowering may increase acute kidney failure
Hyperkalemia	2 646 (4)	–	HR 1.36 (1.01–1.82)	Moderate	Intensive blood pressure lowering may increase hyperkalemia

CI, confidence interval; HR, hazard ratio; OR, odds ratio.
More intensive blood pressure lowering: active blood pressure treatment or intensive blood pressure control.
Less intensive blood pressure lowering: placebo or no treatment or less intensive blood pressure control.

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Table 31.4 Summary of findings: statin therapy.

Outcomes	No. of participants (no. of studies)	Absolute number of patients affected per 1 000 patients treated for 1 year (95% CI)	Relative risk (95% CI)	Certainty of the evidence (GRADE)	Conclusion
Chronic kidney disease stages 3–5					
All-cause mortality	28 276 (13)	5 fewer (2–8 fewer)	0.79 (0.69–0.91)	High	Statin therapy leads to slightly lower mortality
Cardiovascular mortality	19 059 (10)	3 fewer (2–5 fewer)	0.77 (0.69–0.87)	Moderate	Statin therapy leads to slightly lower cardiovascular mortality
Major cardiovascular events	36 033 (16)	6 fewer (4–7 fewer)	0.72 (0.66–0.79)	High	Statin therapy probably leads to slightly lower major cardiovascular events
Myocardial infarction	9 018 (11)	–	0.55 (0.42–0.72)	Moderate	Statin therapy may slightly reduce myocardial infarction
Stroke	8 658 (8)	–	0.62 (0.35–1.12)	Low	It is uncertain whether statin therapy prevents stroke
Elevated creatinine kinase	4 514 (10)	–	0.84 (0.20–3.48)	Low	It is uncertain whether statin therapy leads to elevated creatinine kinase
Liver function abnormalities	7 991 (10)	–	0.76 (0.39–1.50)	Low	It is uncertain whether statin therapy leads to liver function abnormalities

Table 31.5 Summary of findings: antiplatelet therapy.

Outcomes	No. of participants (no. of studies)	Absolute number of patients affected per 1 000 patients treated for one year (95% CI)	Relative risk (95% CI)	Certainty of the evidence (GRADE)	Conclusion
Antiplatelet agents versus placebo or no treatment					
All-cause mortality	16 152 (30)	–	0.95 (0.83–1.07)	Low	It is uncertain whether antiplatelet agents decrease mortality
Cardiovascular mortality	9 337 (19)	–	0.87 (0.65–1.15)	Low	It is uncertain whether antiplatelet agents make any difference to cardiovascular mortality
Myocardial infarction	14 451 (2)	–	0.87 (0.76–0.99)	Low	Antiplatelet agents may prevent myocardial infarction
Stroke	9 544 (14)	–	1.00 (0.58–1.72)	Low	It is uncertain whether antiplatelet agents decrease stroke
Major bleeding	1 592 (27)	–	1.35 (1.10–1.65)	Low	Antiplatelet agents may lead to major bleeding
Minor bleeding	13 106 (3)	–	1.54 (1.26–1.90)	Low	Antiplatelet agents may lead to minor bleeding

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Table 31.6 Summary of findings: glucose-lowering therapy.

Outcomes	No. of participants (no. of studies)	Absolute number of patients affected per 1 000 patients treated for 1 year (95% CI)	Relative risk (95% CI)	Certainty of the evidence (GRADE)	Conclusion
Sodium glucose co-transporter-2 inhibitors versus placebo					
Cardiovascular mortality	4 401 (4)	–	HR 0.70 (0.59–0.82)	Moderate	Sodium glucose co-transporter-2 inhibitors may prevent death
Heart failure	2 519 (6)	–	0.59 (0.41–0.87)	Moderate	Sodium glucose co-transporter-2 inhibitors may reduce heart failure
Hospitalization for heart failure	4 401 (4)		HR 0.61 (0.47–0.80)	Moderate	
Hyperkalemia	2 788 (7)	–	0.58 (0.42–0.81)	Moderate	Sodium glucose co-transporter-2 inhibitors may reduce hyperkalemia
	4397 (4)	–	0.80 (0.65–1.00)	Moderate	
Genital infections	3 086 (10)	–	2.50 (1.52–4.11)	Moderate	Sodium glucose co-transporter-2 inhibitors may increase genital infections
Elevated serum creatinine	848 (7)	–	MD 3.82 μmo/l (1.45–6.19)	Moderate	Sodium glucose co-transporter-2 inhibitors may increase serum creatinine
Acute kidney injury	4 397 (4)		HR 0.85 (0.64 to 1.13)	Moderate	It is uncertain whether sodium glucose co-transporter-2 may increase acute kidney injury
Diabetic ketoacidosis	4 397 (4)		HR 10.80 (1.39–83.65)	Low	It is uncertain whether sodium glucose co-transporter-2 may increase acute kidney injury since the number of diabetic ketoacidosis were low (11 versus 1)
Dipeptidyl peptidase-4 inhibitors versus placebo					
Cardiovascular mortality	5 897 (5)		0.93 (0.77–1.11)	Moderate	Dipeptidyl peptidase-4 inhibitors may have little or no effect on cardiovascular death
Heart failure	–	–	–	Low	It is uncertain whether dipeptidyl peptidase-4 inhibitors prevent heart failure
Metformin verses treatment without metformin					
Chronic kidney disease stages 1–3					
All-cause mortality	33 442 (8)	48 fewer (81–6 fewer)	HR 0.77 (0.61–0.97)	Low	Metformin may prevent death

CI, confidence interval; HR, hazard ratio; MD, mean difference.

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Table 31.7 Summary of findings: anticoagulant therapy.

Outcomes	No. of participants (no. of studies)	Absolute number of patients affected per 1 000 patients treated for 1 year (95% CI)	Relative risk (95% CI)	Certainty of the evidence (GRADE)	Conclusion
Warfarin versus no warfarin					
Chronic kidney disease stages 1–4					
Mortality	34 852 (7)	–	HR 0.65 (0.59–0.72)	Low	Warfarin may reduce risk of mortality
Ischemic stroke or thromboembolism	34 226 (8)	–	HR 0.70 (0.54–0.89)	Low	Warfarin may reduce ischemic stroke or thromboembolism
Major bleeding	33 920 (7)	–	HR 1.15 (0.88–1.49)	Low	It is uncertain whether warfarin increases risk of major bleeding
Direct oral anticoagulant versus warfarin					
Stroke and systemic embolism events	12 545 (8)	–	0.81 (0.65–1.00)	Moderate	Direct oral anticoagulant probably reduces the incidence of stroke and systemic embolism events compared to warfarin
Major bleeding events	12 521 (8)	–	0.79 (0.59–1.04)	Moderate	Direct oral anticoagulant slightly reduces the incidence of major bleeding compared to warfarin

CI, confidence interval; HR, hazard ratio.

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Table 31.8 Summary of findings: coronary revascularization.

Outcomes	No. of participants (no. of studies)	Absolute number of patients affected per 1 000 patients treated for 1 year (95% CI)	Relative risk (95% CI)	Certainty of the evidence (GRADE)	Conclusion
Drug-eluting stents versus bare-metal stents					
All-cause mortality	91 046 (30)	–	0.77 (1.71–1.84)	Low	Drug-eluting stents probably lead to lower mortality than bare-metal stents
Cardiovascular mortality	5 045 (17)	–	0.51 (0.38 to 0.70)	Low	Drug-eluting stents may prevent cardiovascular mortality more than bare-metal stents
Myocardial infarction	64 389 (24)	–	0.90 (0.86–0.95)	Low	Drug-eluting stents may prevent myocardial infarction more than bare-metal stents
Target-vessel revascularization	10 029 (19)	–	0.61 (0.47–0.80)	Low	Drug-eluting stents may prevent target-vessel revascularization more than bare-metal stents
Stent thrombosis	6 714 (2)	–	0.75 (0.55–1.01)	Low	Drug-eluting stents probably lead to lower stent thrombosis than bare-metal stents
Percutaneous coronary intervention with drug-eluting stents versus coronary artery bypass grafting					
Short-term all-cause mortality	25 444 (9)	–	OR 0.33 (0.29–0.38)	Low	Percutaneous coronary intervention with drug-eluting stents may lead to lower short-term mortality than coronary artery bypass grafting
Long-term all-cause mortality	28 521 (14)	–	OR 1.22 (1.15–1.29)	Low	Percutaneous coronary intervention with drug-eluting stents may lead to higher long-term mortality than coronary artery bypass grafting
Heart-related mortality	19 104 (9)	–	OR 1.29 (1.20–1.38)	Low	Percutaneous coronary intervention with drug-eluting stents may lead to higher heart-related mortality than coronary artery bypass grafting
Myocardial infarction	10 579 (12)	–	OR 1.89 (1.11–3.21)	Low	Percutaneous coronary intervention with drug-eluting stents may lead to higher myocardial infarction than coronary artery bypass grafting
Repeat revascularization	28 530 (14)	–	OR 3.47 (2.57–4.69)	Low	Percutaneous coronary intervention with drug-eluting stents may lead to higher repeat revascularization than coronary artery bypass grafting
Cerebrovascular accident	9 319 (9)	–	OR 0.64 (0.51–0.80)	Low	Percutaneous coronary intervention with drug-eluting stents may lead to lower cerebrovascular accident than coronary artery bypass grafting.
Major adverse heart-related and cerebrovascular events	3 420 (8)	–	OR 2.00 (1.39–2.89)	Low	Percutaneous coronary intervention with drug-eluting stents may lead to higher major adverse heart-related and cerebrovascular events than coronary artery bypass grafting

CI, confidence interval; OR, odds ratio.

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Blood Pressure Control

CKD patients have high prevalence of hypertension. Blood pressure lowering may be an important strategy to prevent CVD in CKD patients. Blood pressure lowering reduced the risk of major cardiovascular events in a meta-analysis of 26 randomized trials, which included 30 295 CKD subjects [4]. The effect in reducing CVD was similar among subjects with or without CKD. There was no significant difference in the effect on cardiovascular events between angiotensin converting enzyme inhibitors, calcium channel blockers, or diuretics or β blocker based treatment. Compared to less intensive blood pressure lowering, intensive blood pressure lowering was associated with lower mortality in patients with CKD stages 3–5 in the meta-analysis of 18 randomized clinical trials [5]. However, there was not enough data to define the target blood pressure for the prevention of CVD in CKD patients. In the subgroup analysis of 2646 CKD patients in the Systolic Blood Pressure Intervention Trial (SPRINT), the target blood pressure <120 mmHg (intensive group) was compared to <140 mmHg (standard group) for the median follow-up of 3.3 years [6]. The intensive group had a lower rate of all-cause mortality and higher AKI as an adverse clinical event. In the analysis of 9361 patients in SPRINT, the risk factors for AKI were older age, non-Caucasian, lower baseline eGFR, and presence of CVD at baseline [100]. Intensive blood pressure lowering may be suggested to prevent mortality, but careful monitoring of kidney function is necessary in CKD patients, especially among patients with older age or previous CVD.

Statins

Meta-analysis of 50 studies, which includes 45 285 nondialysis CKD patients, comparing the effects of statins on mortality, cardiovascular events, and adverse events, was performed [7]. Compared to placebo, statin therapy reduced all-cause mortality, cardiovascular mortality, major cardiovascular events, and myocardial infarction, but the effect on stroke or risk of related adverse events was uncertain in nondialysis CKD. The statin therapy had little or no effect on mortality or cardiovascular events in CKD patients on dialysis [8]. The effect of statin therapy on mortality or CVD was uncertain in kidney transplant recipients [9].

Antiplatelet Therapy

The effect of antiplatelet therapy in risk reduction of CVD in CKD patients is not confirmed. In the meta-analysis of 30 trials, antiplatelet therapy reduced myocardial infarction but the effect on mortality and increased bleeding was uncertain compared to placebo or no treatment [10]. The platelet dysfunction in CKD patients may be responsible for reduced effect of antiplatelet therapy [101].

Glucose Control

It is not clear whether intensive glucose control is effective in reducing CVD in CKD patients with diabetes [102]. In a meta-analysis of 44 studies, which included 13 036 patients, the effect of glucose lowering therapy in CKD patients with diabetes mellitus was examined [11]. Sodium-glucose co-transporter-2 (SGLT2) inhibitors reduced heart failure but increased genital infection and serum creatinine. SGLT2 probably had little or no effect on cardiovascular mortality. Dipeptidyl peptidase-4 (DPP4) inhibitors had little or no effect on cardiovascular mortality. There was not enough data to examine the effect for other classes of glucose lowering therapy. In the double-blind, randomized Canagliflozin and Renal Events in Diabetes and Established Nephropathy Clinical Evaluation (CREDENCE) trial, oral SGLT2 inhibitor canagliflozin or placebo were assigned to 4401 patients with type 2 diabetes and albuminuric kidney disease [12]. After a median follow-up of 2.6 years, the relative risk of composite kidney outcome was lower by 34%. The risk of cardiovascular death, myocardial infarction, or stroke and hospitalization for heart failure was also lower. Trials of these newer glucose lowering medications (SGLT2, DPP4, and glucagon-like peptide-1 receptor agonist) on cardiovascular outcomes in patients with diabetes and CKD are underway [102].

Metformin reduced all-cause mortality in CKD patients with diabetes in the meta-analysis of 33 442 patients in seven studies [103]. Metformin is not recommended in patients with low kidney function (eGFR <30 ml/min/1.73 m^2) because of the risk of metformin-associated lactic acidosis. A systematic review was performed to examine the risk of metformin-associated lactic acidosis, which suggested that an increased risk of lactic acidosis in metformin-treated patients with CKD may be limited [104]. Metformin may be used in patients with mild to moderate CKD (eGFR 30–60 ml/min/1.73 m^2), but dose adjustment and careful follow-up of kidney function are recommended (when the kidney function declined to eGFR <45 ml/min/1.73 m^2).

Anticoagulant

In patients with CKD and atrial fibrillation, anticoagulant therapy may be suggested to prevent thromboembolism and stroke. The risk of major and minor bleeding must be considered. In a meta-analysis of 11 cohort studies, warfarin therapy reduced the risk of ischemic or thromboembolism and mortality [13]. There was no significant effect on

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risk of major bleeding in CKD without ESRD, but there was increased risk of major bleeding in CKD with ESRD.

Direct oral anticoagulants (DOAC) have been developed and are used as an alternative therapy to warfarin. In a meta-analysis of five studies which included 12 545 CKD patients with atrial fibrillation, the effect of DOAC was examined [14]. DOAC therapy reduced incident stroke and systemic embolism and may slightly reduce major bleeding events compared to warfarin therapy. The use of DOAC in CKD stage 5D with atrial fibrillation was not determined due to the lack of high-quality data [105].

Coronary Revascularization

CKD patients with CAD may need myocardial revascularization. In percutaneous coronary intervention (PCI), a bare metal stent (BMS) or drug-eluting stent (DES) is used. Most clinical trials of PCI exclude CKD patients. Using 31 observational or randomized clinical studies with 91 817 patients, the outcome with BMS or DES was evaluated in CKD patients [15]. DES implantation was associated with lower all-cause mortality, cardiovascular mortality, myocardial infarction, and target-vessel revascularization.

Coronary artery bypass grafting (CABG) is another strategy for coronary revascularization. The benefits of PCI or CABG treatment differs, and the outcome may differ in CKD patients compared to non-CKD patients with CAD. In a meta-analysis of 11 studies with 29 246 patients with CKD and multivessel disease, the outcome of PCI with DES and CABG was examined [16]. Compared to CABG, PCI with DES had higher long-term all-cause mortality, cardiac mortality, myocardial infarction, repeat revascularization, and major adverse cardiovascular events, but PCI with DES had lower short-term all-cause mortality and cerebrovascular events.

Lifestyle Modification

Lifestyle modifications are suggested in CKD patients to prevent CVD, but the evidence is mostly from derived observational study or small clinical trials [94]. The recommendations include smoking cessation, exercise, and weight loss, but the effect on CVD prevention in CKD patients is not confirmed.

Physical exercise in CKD patients was associated with improved physical fitness, walking capacity, and cardiovascular dimensions, which include resting systolic and diastolic blood pressures and heart rates [106]. The effect of weight loss intervention was examined in a small number of CKD patients in short duration studies [107]. In a meta-analysis of 13 studies, nonsurgical weight loss reduced proteinuria and blood pressure. The long-term effect on CVD in CKD patients is unknown.

Reduced dietary salt was associated with small reduction in systolic and diastolic blood pressure in normotensive subjects, and greater reduction of systolic blood pressure and no change in diastolic blood pressure in hypertensive subjects [108]. In CKD patients, salt restriction reduced systolic and diastolic blood pressure [17]. The long-term effect of salt restriction on CVD in CKD patients is unknown. The effect of low protein diet in CKD patients without diabetes was examined in the meta-analysis of 10 studies [18]. Low protein diet probably has little or no effect on mortality compared to normal protein diet.

Conclusion

CVD is the major cause of morbidity and mortality in CKD patients. Increased risk of CVD in CKD patients is due to traditional and nontraditional risk factors, some of which are specific to CKD.

Many RCTs excluded CKD patients and therefore the evidence to support the clinical practice of CKD is based on insufficient and low-quality evidence. Due to the difficulty in diagnosis of CVD in CKD patients, CKD patients are less likely to receive evidence-based medicine, and the prognosis tends to be poor compared to non-CKD patients. The adjusted criteria for the diagnosis and treatment of CVD in CKD patients based on the best available recommendations may improve outcomes.

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Infection and CKD

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Introduction

Nephrologists are familiar with treating dialysis patients with access infections or peritonitis. Nephrologists are also familiar with the multitude of infectious complications seen in immunosuppressed patients, such as those with vasculitis and those who have received a kidney transplant. However, the vast majority of people with chronic kidney disease (CKD) are seen by general physicians and other specialist doctors, and nephrologists will often be asked on ways to prevent infections and address complications in this broader group of patients, many of whom do not have a specified diagnosis as an underlying cause of CKD.

In this chapter, we discussed the relevant evidence to support management of infectious complications associated with CKD. The focus is on patients with CKD (not on kidney replacement therapy), but frequently evidence to support treatment decisions has been extrapolated from those on dialysis therapy to those on CKD.

This chapter covers what is known about the risk of infection, reasons for the higher infection risk, the risk of infection-associated complications, and how to prevent and treat infections among patients with CKD (Table 32.1). Much of the data on infections as a complication of CKD derives from high-income countries. Due to limited information on whether CKD predisposes to infections that are predominant in low-income settings such as malaria or human immunodeficiency virus (HIV), these conditions are not discussed. Additional infection-related topics are covered in other chapters: infections as a complication of hemodialysis (Chapter 43), peritoneal dialysis (Chapter 48), and transplantation (Chapter 59), and infections which may cause CKD (Chapter 20 and 26).

CKD and Risk of Developing Infections

A 2014 systematic review of CKD and infection risk found 14 studies comparing incidence of infection among people with CKD to the incidence among people without known history of CKD [2]. Figure 32.1 displays the associations of CKD with infection risk. Studies that systematically excluded patients receiving dialysis are grouped separately from studies in which patients receiving dialysis were, or may have been, included together with patients with CKD. Seven studies were set among the general population, and the remainder in higher risk populations (e.g. patients seen in kidney clinics, with diabetes, or of older age). Although a range of infections were investigated, most required hospital admission or blood culture. Unsurprisingly in view of the range of infection outcomes investigated and the diversity of how kidney disease was defined, there was great heterogeneity ($I^2 = 96.5\%$) and no meta-analysis was performed. Nevertheless, all point estimates and most confidence intervals (CIs) suggest a strong and graded association of infection risk with CKD and its severity.

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Table 32.1 Chronic kidney disease and infection risk: KDIGO recommendations [1].

Intervention	Recommendation	Certainty of evidence	Strength of recommendation[a]
Antibiotic prescribing	Dosing must take the patient's impaired kidney function into consideration by adjusting the dosing interval (if the drug effect depends on concentration, e.g. aminoglycosides) or dose level (for drugs which require constant levels such as beta-lactams) or considering a nonrenally cleared alternative Consider drug interactions and follow local guidelines to minimize antimicrobial resistance	*Moderate to high* Evidence of drug levels mainly from pharmacokinetic and pharmacodynamics studies with strong observational post-marketing evidence of drug side effects for older drugs Literature on preventing antimicrobial resistance is focused on overall prescribing irrespective of CKD status (unless there is a concern about toxicity or efficacy)	Strong (1A)
Annual vaccination against influenza	KDIGO recommend that all adults with CKD are offered annual vaccination with inactivated influenza vaccine, unless contraindicated [1]	*Low* Extrapolation from observational data analysis. To date there is no/limited evidence of vaccine efficacy for CKD stages specifically. However, given that the vaccine is known to be efficacious in older population overall, amongst whom a sizable proportion have some degree of CKD, there appears overall benefit, especially considering the high rate of infection-related hospitalization for those with CKD. Live-attenuated influenza vaccination has not been tested in patients with CKD.	Strong (1B)
Vaccination with polyvalent pneumococcal vaccine	KDIGO recommend that all adults with eGFR < 30 ml/min/1.73 m^2(GFR categories G4–G5) and those at high risk of pneumococcal infection (e.g. nephrotic syndrome, diabetes, or those receiving immunosuppression) receive vaccination with polyvalent pneumococcal vaccine unless contraindicated [1]	*Low* There are limited observational data on vaccination efficacy by CKD stages. However, given that the vaccine is known to be efficacious in older population overall, amongst whom a sizable proportion have some degree of CKD, there appears overall benefit, especially considering the high rate of infection-related hospitalization for those with CKD.	Strong (1B)
Repeat vaccination with polyvalent pneumococcal vaccine within 5 years	KDIGO recommend that all adults with CKD who have received pneumococcal vaccination are offered revaccination within 5 years [1]	*Low* There are limited data to support a particular revaccination scheme, but in advanced CKD antibody response is less marked and titres decline faster than for people with normal kidney function	Strong (1B)
Immunization against hepatitis B	KDIGO recommend that all adults who are at high risk of progression of CKD and have GFR > 30 ml/min/1.73 m^2 (GFR categories G4–G5) be immunized against hepatitis B and the response confirmed by appropriate serological testing [1]	*Moderate* Those with higher eGFR have shown better seroconversion in response to hepatitis B vaccine	Strong (1B)
Use of live vaccines	Consideration of live vaccine should include an appreciation of the patient's immune status and should be in line with recommendations from official or governmental bodies [1]	*Very low* Due to the fact that people with CKD are often immunocompromised to some degree, as evidenced from observational data analysis, there may be a risk of vaccine-related disease	Not graded
Vaccination in children	Pediatric immunization schedules should be followed according to official international and regional recommendations for children with CKD [1]	*Very low* As pediatric kidney disease is rare, there are no or very limited data on this topic	Not graded

[a] Level of strength of recommendation as per the KDIGO recommendations: Level 1, We recommend; Level 2, We suggest. Letter grading refers to quality of evidence: A, High; B, Moderate.
Source: Adapted with permission from Kidney Disease: Improving Global Outcomes CKD Work Group [1].

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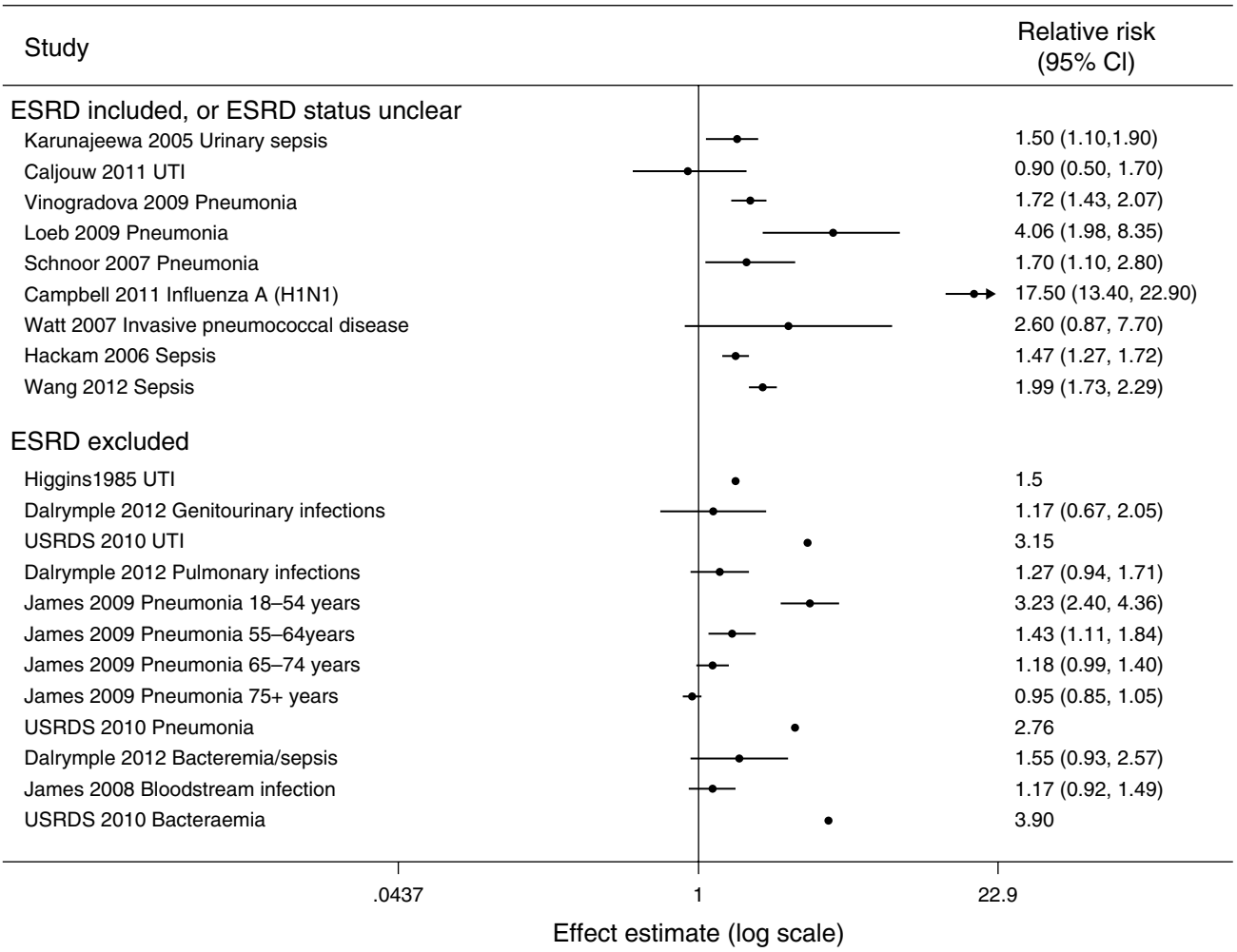

Figure 32.1 Forest plot of all estimates of the association of chronic kidney disease with infection risk (n = 17) from all 14 studies identified. The estimates from Higgins 1985 and USRDS 2010 did not include SEs. Dalrymple 2012: presented estimates compare eGFR 45–59 with eGFR ≥90 ml/min/1.73m^2; James 2009: presented estimates compare eGFR 45–59 with eGFR 60–104 ml/min/1.73m^2; James 2008: presented estimates compare eGFR 45–59 with eGFR≥60 ml/min/1.73m^2. eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; USRDS, US Renal Data System; UTI, urinary tract infection. *Source:* From McDonald et al. [2].

Since this systematic review, there have been a further five studies investigating the association of CKD (defined using estimated glomerular filtration rate [eGFR]) with a range of infections, from the United States [3], Sweden [4], and the UK [5–7]. The results were all consistent with the previous evidence of a graded association between CKD and increased risk of infection.

Most of the available studies of infection in people with CKD have looked at severe infection or hospitalization with infection, such as those of James and colleagues from 2008 to 2009 [8, 9]. These studies used laboratory-confirmed CKD and investigated severe community-acquired infection (sepsis and hospitalization with pneumonia), taking into account underlying comorbidities. Notably, while underlying comorbidity did explain some of the underlying risk, adjustment for the comorbidity did not explain this association fully.

As people with CKD are often multimorbid and frail, it is perhaps unsurprising that people with CKD are more likely to experience severe infections such as sepsis or pneumonia requiring hospitalization. These associations could be due to increased severity of infection rather than increased risk. However, some studies have investigated the association of CKD with community-acquired infection, including infection diagnosed and treated in the community. This approach more fully quantifies the burden of community-acquired infection, an important and common problem, but also isolates the impact of CKD on increased infection risk, distinct from the impact on infection severity.

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Studies of infections in primary care have identified associations between lower eGFR and increased risk of a range of infections, including pneumonia, urinary tract infections (UTI), sepsis, skin/soft tissue infections, and gastrointestinal tract infections [4, 5, 10, 11]. Table 32.2 summarizes two studies of community-acquired infection. The Swedish study [4] was set among a cohort of all patients from Stockholm Region with a creatinine laboratory result available. It studied a range of community-acquired infections and showed that there was a graded increase in the risk of community-acquired infections as eGFR declined. Lower respiratory tract infections, UTIs, and sepsis became more common as a percentage of total recorded infections as eGFR declined. An association with skin/soft tissue infections and gastrointestinal tract infections was also observed. No association was found with nervous system and upper respiratory tract infections. The UK study [5] used a similar design among older people with diabetes, who have complete kidney function data due to incentivized testing for kidney function among these patients in the UK. Both the Swedish and the UK study adjusted for underlying comorbidities, which again did not fully explain the associations noted.

In addition to a graded association between eGFR and risk of community-acquired lower respiratory tract infections (LRTI) and sepsis, proteinuria was also independently associated with increased risk of both these community-acquired infections – this is in line with what was seen for severe infections requiring hospitalizations in the atherosclerosis risk in communities (ARIC) study [3].

The observed association between CKD and UTI may need to be interpreted with caution. Recurrent UTIs are very common and frequently require hospitalization among people with CKD. There is a risk that those who have had previous infections may have more frequent assessment for kidney function and repeat UTI. There may also be a particular group of patients in whom the recurrent UTIs have caused CKD, which in turn predisposes them to more infections. Both these issues introduce a problem of reverse causality into the data. While it is evident that UTIs are common among people with CKD, it is not clear whether or to what extent CKD causes UTIs.

In summary, infections are common among people with CKD and the risk of infection increases as kidney function declines. Infections pose a substantive burden to secondary care as people with CKD are likely to require hospitalization owing to the severity of infection, especially with sepsis and severe LRTI. Neither the associations with hospitalization and severe infections, nor those with infections diagnosed and treated in the community, were fully explained by adjustment for comorbidities. Hence, there seems to be a biological association by which the presence of CKD increases the susceptibility to infection risk as well as severity. How this arises will be discussed in the next section.

CKD and Susceptibility to Infection

As discussed above, patients with CKD are at greater risk of infection, even well before any exposure to kidney replacement therapy and its attendant complications [12–16]. This may be due to multiple underlying risk factors, or due to treatment for the kidney disease, or a phenomenon related to reduced immunity as kidney function declines irrespective of the cause of kidney disease. We discuss each of these in turn.

One risk factor that may be underlying the risk of observed infection is having had a previous infection. For

Table 32.2 Studies investigating the associations between CKD and risk of community-acquired infections using electronic health records (since 2014).

Studies of community-acquired infections					Crude IR	RR for eGFR categories in ml/min/1.73m^2 (95% CI)				
Author	Year	Country	Population studied	Outcome	Per 1000 person-years	eGFR 60+	eGFR 45–59	eGFR 30–44	eGFR 15–30	eGFR <15
Xu [4]	2017	Sweden	General population	all infections	95	1	1.08 (1.01–1.14)		1.53 (1.39–1.69)	
McDonald [5]	2015	UK	Diabetes	LRTI	155.8	1	1.03 (1.01–1.04)	1.08 (1.05–1.10)	1.17 (1.13–1.22)	1.47 (1.34–1.62)
				Pneumonia	10.3	1	0.95 (0.89–1.01)	1.19 (1.11–1.28)	1.73 (1.57–1.92)	3.04 (2.42–3.83)
				Sepsis	2.5	1	1.11 (0.99–1.25)	1.51 (1.32–1.73)	2.50 (2.08–3.00)	5.56 (3.90–7.94)

RR, risk ratio; IR, incidence rate; 95% CI, 95% confidence interval; LRTI, lower respiratory tract infection.

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some patients, CKD is a direct result of infection, from recurrent UTIs, to HIV and tuberculosis (TB). However, for the majority of patients with CKD, old age, underlying, or comorbid disease and lifestyle factors, such as diabetes and smoking, are independent risk factors for infection. With regards to old age, the term immunosenescence has been used to describe the changes in immune function that make older people more susceptible to infection [17], mainly via reduced response to vaccination via impaired T-cell function and the interplay of T cells with other parts of the immune system. Diabetes itself is a known risk factor for serious bacterial infections [18], and glycemic control a main risk factor for developing infections and requiring hospitalization with infections [19]. Smoking is a risk factor common to CKD and bacterial and viral infection. Nevertheless, as discussed above, even taking these factors into account, an increased risk of community-acquired infections is consistently observed as eGFR declines.

Treatment for CKD and underlying diseases with steroids and immunosuppressants can further predispose to infection. However, the vast majority of people with CKD in the general population do not have treatment with immunosuppressants or severely immunocompromising disease. Instead, the most common underlying conditions are old age, diabetes, a history of smoking, and exposure to infectious agents from frequent healthcare attendance [12].

CKD itself may have a causal role in increased infection risk through additional disturbance of both innate and adaptive immunity. Chronic inflammation, proteinuria, and uremia may each play separate roles. There are multiple potential mechanisms for CKD to alter cell-mediated and humoral immune system function. A number of observational studies have considered factors such as malnutrition, hypoalbuminemia, anemia, complement loss, disrupted calcium regulation and vitamin D insufficiency, and chronic kidney inflammation [12, 20]. Some of these factors, such as anemia, malnutrition, and low vitamin D, may be modifiable with good clinical care. However, before advocating replacement of vitamin D or treatment of anemia to prevent infections, clinicians should remember that lack of vitamin D and anemia may simply be markers of severity of overall illness and that treating these may fail to change, or possibly even increase, infection risk. For example, vitamin D is a marker of sun exposure, and bed-bound patients may be less likely to be out in the sun, so any observational study is likely confounded by disease severity. A review of existing trials of vitamin D supplementation to prevent acute respiratory infections suggests a potential role for patients with very low vitamin D levels [21]. At present, there are ongoing trials to test whether vitamin D supplementation improves outcomes, including infections in the CKD and dialysis population. In considering anemia as a potential mediator of infection risk, those patients with severe anemia tend to be most multimorbid, and anemia may be a marker of underlying chronic infection. Moreover, anemia of chronic illness may be a result of a physiologic process by which the body tries to sequester iron (with resulting anemia) to prevent increased infection risk [22]. Again, we have to wait for the results from randomized trials to determine whether treating anemia indeed reduces infection risk – it may well be the opposite as intravenous iron can cause an increased risk of infection [23].

As CKD worsens, a reduced response of the adaptive immune system has been observed in the context of a reduced response to vaccinations [24, 25]. This impairment may be in part driven by uremic toxins [26], which impair the T-lymphocyte dependent response (required to respond to vaccinations) [27] and also the phagocytosis response of polymorphonuclear lymphocytes [28, 29]. This reduced response to vaccination itself further increases the risk of vaccine-preventable infections.

Figure 32.2 illustrates that the association between CKD and susceptibility to infection is likely driven by a combination of the patient population's age and comorbidities, together with a likely impairment of the adaptive immune system caused by CKD.

Complications of Infections among People with CKD

We review below a number of key complications of infection that are relevant to people with CKD, including mortality, acute kidney injury (AKI), progression to dialysis, and cardiovascular disease. These associations highlight that infections should not be taken lightly, as they may have serious consequences.

Mortality

There is a graded association of CKD with mortality risk from infection. The rate of infection-related mortality and the proportion of deaths due to infection increase as eGFR declines among the general population [3, 30–32]. During 13 years of follow-up in the National Health and Nutrition Examination Survey study (NHANES) study, death from infection occurred in 1.2% of the population with normal eGFR, increasing to 4.6% in those with eGFR 45–59 ml/min/1.73m^2 and 10.3% in those with eGFR < 45 ml/min/1.73m^2. Compared to people with eGFR ≥60 ml/min/1.73m^2, the corresponding hazards of infection-related mortality were 1.36 (95% CI 0.81–2.30) and 2.36-fold (1.04–5.38) higher for eGFR of 45–59 and <45 ml/min/1.73m^2,

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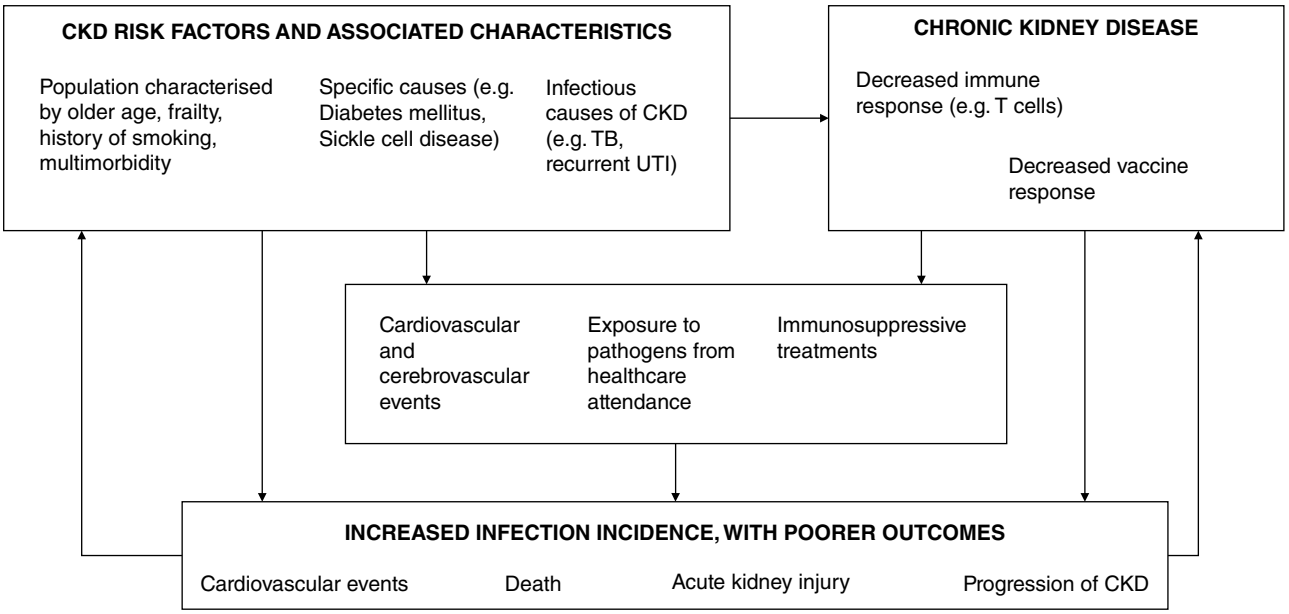

Figure 32.2 Risk factors and outcomes of infection in chronic kidney disease.

respectively [32]. Influenza/pneumonia and sepsis are the infections that most commonly cause death in patients with CKD [31]. The graded association of lower kidney function with higher infection-related mortality is repeated in the older population [8, 9, 33, 34], those with diabetes [35], and among older adults resident in nursing homes [34].

The increased risk of death is not simply due to increased risk of acquiring infection. If a patient gets admitted with infection, the presence of CKD worsens their outlook considerably. Several studies show that among those hospitalized with any infection, lower kidney function is associated with higher in-hospital mortality [36] and subsequent long-term all-cause mortality [37] (Table 32.3). The crude mortality rates are significant. In those hospitalized with sepsis/bloodstream infection, 20–22% of patients with eGFR < 60 ml/min/1.73m^2 died in hospital [36, 43], 49–70% died within 28 days [39, 41, 42], 62% died within 90 days [42], and 82% died within a year [39]. In those hospitalized with pneumonia, 9–19% of patients with eGFR < 60 ml/min/1.73m^2 died in hospital [36, 38], 29–47% died within 28 days [42], and 36–53% died within 90 days [42]. In a study enrolling patients hospitalized with infection at four hospitals in China, heightened risks of mortality were greatest in the first 7 days following admission and progressively declined thereafter, but remained significantly elevated at a year following admission [37]. This increased mortality risk can be seen also for infections other than sepsis and pneumonia. In a retrospective Japanese cohort study enrolling patients with smear-positive pulmonary tuberculosis, eGFR of <30 ml/min/1.73m^2 was a risk factor for death with adjusted odds ratio 2.99 (95% CI 1.20–7.51) [40]. In a systematic review of 19 studies of *Clostridium difficile* infection, a pooled analysis of 116 875 patients found the mortality risk associated with CKD was 1.76 (95% CI 1.26–2.47) [44].

For patients with CKD, the implication of an infection for longer term prognosis is also considerable. In a Canadian prospective cohort (CanPREDDICT) of patients with advanced CKD (eGFR 15–45 ml/min/1.73m^2) followed for up to 5 years, those who experienced an infection had over three times increased risk of mortality than those without infection (hazard ratio 3.39, 95% CI 2.65–4.33) [45].

AKI and Increased Risk of Progression to ESKD

It is well established that infection, especially severe infection such as sepsis, increases the risks of AKI and of requiring kidney replacement therapy [46]. Among those with AKI, 86.9% cases were attributed to sepsis or hypovolemia [47]. When an infection occurs, underlying kidney function impairment increases the risk of AKI. In septic shock, patients with CKD (59.5%) had a higher risk of AKI than those without CKD (40.8%) [48]. Among patients infected with influenza A, 67–69% of patients with CKD had AKI [49, 50]. However, there are other studies that have not found associations between CKD and AKI risk in infection [51, 52].

An infection in the context of advanced CKD can propel patients onto dialysis. In the CanPREDDICT study of patients with advanced CKD (eGFR 15–45 ml/min/1.73m^2), those with infection had a 58% increased risk of end-stage kidney disease (ESKD) (hazard ratio 1.58, 95%

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Table 32.3 Risk of death in people with infection by level of kidney function (baseline eGFR).

Identity	Region	Type of infection	Study population	Number of subjects	Age (mean ± SD, medium [quartile])	Kidney function (eGFR: ml/min/1.73 m^2)	Outcome	Number with outcome	Crude risk (%)	Relative risk
For those with infection (sepsis, pneumonia, etc.), how does reduced renal function increase risk of death?										
Viasus et al. [38]	Spain	Pneumonia	Hospitalized with pneumonia	3597	70 [56–79]	≥60	In-hospital mortality	290	8.30	NA
				105	77 [67–84]	30–59		16	15.20	
				42		15–29		8	19.00	
				10		<15		1	10.00	
Maizel et al. [39]	France	Septic shock	Patients with septic shock in the Medical ICU	107	63 [54–76]	≥60	28-day mortality	54	50	1 (ref)
				56	72 [62–79]	<60		39	70	aHR 1.7 (1.08–2.68)
Igari et al. [40]	Japan	Smear-positive pulmonary tuberculosis	Patients (12–99 years) hospitalized for tuberculosis	499	62.1 (19.4)	≥60	Death	62	12.40	NA
				629		<60		93	14.80	NA
Mansur et al. [41]	Germany	Sepsis	Adult patients admitted to surgical ICU	426	63 (15)	No-CKD	Survival up to 90 days	Not reported	27	1 (ref)
				56		CKD (unclear definition)		Not reported	54	aHR 2.25 (1.46–3.46)
McDonald et al. [42]	England	Pneumonia	People aged ≥65 years with diabetes mellitus and community-acquired pneumonia or sepsis	2531	78 [72–83]	≥60	28-day mortality	687	27.10	1 (ref)
				1162	82 [77–87]	45–60		332	28.60	aOR 0.93 (0.85–1.04)
				764		30–44		265	34.70	aOR 0.99 (0.88–1.12)
				286		<30		122	42.70	aOR 1.30 (1.12–1.52)
		Sepsis		566	76 [71–82]	≥60	28-day mortality	179	31.60	1 (ref)
				232	81 [75–86]	45–60		76	32.80	aOR 0.91 (0.72–1.14)
				190		30–44		88	46.30	aOR 1.24 (0.99–1.54)
				70		<30		34	48.60	aOR 1.37 (1.05–1.79)
Neyra et al. [43]	USA	Sepsis	ICU adults with severe sepsis or septic shock	1421	Not reported (around 62)	>60	In-hospital mortality	339	23.90	NA
				1211	Not reported (around 70)	15–59		264	21.80	

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Su et al. [36]	China	Overall	Adult (>18 years) hospitalized with infection	4348	66 [53–77]	≥60	In-hospital mortality	239	5.50	1 (ref)
				1935	77 [68–83]	<60		235	12.20	aOR 2.01 (1.34–3.02)
		Bloodstream infections or sepsis		129	Not reported	≥60		23	17.80	1 (ref)
				80		<60		16	20.00	aOR 0.93 (0.35–2.48)
		Pneumonia		1447		≥60		111	7.67	1 (ref)
				774		<60		72	9.30	aOR 1.04 (0.73–1.51)
		Urinary tract infections		875		≥60		7	0.80	1 (ref)
				818		<60		18	2.20	aOR 2.26 (0.58–8.77)
Su et al. [37]	China	Any infection-related hospitalization	Adult (>18 years) hospitalized with infection	32 388	57 [42–70]	≥60	All-cause death for a follow-up of median 2.39 years	2964	NA	1 (ref)
				5527	77 [66–82]	30–59		1088		aHR 1.19 (1.11–1.28)
				2609	71 [58–80]	<30		729		aHR 1.73 (1.59–1.88)

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CI 1.22–2.05) [45]. In a population-based retrospective cohort study from Taiwan's National Health Insurance Research Database, the overall incidence rate ratio of ESKD adjusted for competing mortality was 23% higher in those with pneumococcal pneumonia than in those without pneumococcal pneumonia ((crude ESKD rates 5.26 vs. 3.10 per 1000 person-years), with an adjusted sub-hazard ratio of 1.14 (95% CI 1.01–1.29) [53].

Cardiovascular Events

It is well known that for the general population acute infections can lead to an acute but temporary increase in the risk of arterial and venous thrombotic events [54, 55]. Downstream effects of acute infections include dysfunction of endothelial, redox, and coagulation systems, all of which occurs in the face of diminished cellular oxygen availability, cytokine storm, sympathetic overload, complement activation, and vasoconstriction of some vascular beds (including that of the kidney) [14, 56, 57]. The CanPREDDICT study of patients with advanced CKD (eGFR 15–45 ml/min/1.73m^2) found that those with an episode of infection had an increased risk of cardiovascular ischemia (hazard ratio 1.80, 95% CI 1.24–2.60) and congestive heart failure (HR 3.22, 95% CI 2.25–4.61) [45].

In summary, kidney dysfunction worsens prognosis in those who present with infection, while infection worsens kidney function acutely and may propel people with advanced CKD onto dialysis. Most important though is the considerable risk of mortality if a person with reduced kidney function is hospitalized with infection. In the case of sepsis, which is known to be more common among people with CKD, there is clear evidence that early recognition and treatment can improve outcomes. Patients with CKD should be advised to seek help early when they have symptoms of infections.

Preventing and Treating Infections among People with CKD

Preventing Infections in CKD

Vaccination is the best strategy for preventing morbidity and mortality from infection, and is vital among this high-risk population. Vaccines particularly relevant for patients with CKD are considered below: pneumococcal and inactivated influenza vaccinations are recommended for patients with CKD, and patients awaiting dialysis or kidney transplant are recommended to be vaccinated against hepatitis B and may benefit from varicella or herpes zoster vaccination [1, 58].

Most research into vaccination in kidney disease has focused on patients with ESKD [59]. Since immune responsiveness declines progressively with worsening kidney function, evidence of vaccine effectiveness and safety among patients with ESKD is included where necessary to indicate likely effectiveness or safety for patients with CKD. Vaccination guidance for kidney transplant recipients and patients with end-stage renal disease (ESRD) is covered in other chapters and should be consulted separately, in particular noting advice on live and live-attenuated vaccines.

Pneumococcal Vaccine

Streptococcus pneumonia is the most common cause of community-acquired pneumonia, which causes a high burden of mortality and morbidity among patients with CKD [5, 42, 60]. Systematic reviews of the effectiveness of pneumococcal vaccine in the general population have been hampered by heterogeneity [61], which may be attributable to varying lengths of follow-up as immunity wanes over time [62]. An observational study that explored how predialysis CKD related to vaccine effectiveness among people aged ≥65 years with diabetes found some evidence that vaccine effectiveness was lower among patients with a history of proteinuria ($P = 0.04$), but no evidence of variation according to eGFR. Vaccine effectiveness was 22% (95% CI 11–31%) in the first year after vaccination, but was negligible after 5 years [63].

Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend that all adults with eGFR < 30 ml/min/1.73 m^2 (glomerular filtration rate (GFR) categories G4-G5) and those at high risk of pneumococcal infection (e.g. nephrotic syndrome, diabetes, or those receiving immunosuppression) receive vaccination with polyvalent pneumococcal vaccine unless contraindicated, and that all adults with CKD who have received pneumococcal vaccination are offered revaccination within 5 years [1]. UK guidelines recommend vaccination every 5 years with 23-valent pneumococcal polysaccharide vaccine for children and adults with nephrotic syndrome, CKD stages 4 and 5, and those on kidney dialysis or with kidney transplantation [58].

Influenza

Influenza vaccination has the potential to reduce morbidity and mortality from both influenza and pneumonia. Up to one-third of community-acquired pneumonia may be influenza-related, due to bacterial co-infection or secondary bacterial pneumonia [64]. A 2014 systematic review of influenza vaccination among patients with ESKD found five observational studies, none of which included safety

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data, and concluded that the evidence on effectiveness was limited and of low quality [65]. One of the included studies is often cited as evidence that influenza vaccination is effective in ESKD; in this observational study of US Medicare patients receiving dialysis, influenza vaccination was associated with lower risk of hospitalization and death [66]. However, McGrath et al. found that US Medicare patients receiving hemodialysis were less likely to be vaccinated if they had frequent or longer hospitalizations or required skilled nursing, suggesting an overestimation of the effectiveness of influenza vaccination in this dataset due to a "healthy vaccinee" effect [67]. When McGrath et al. adjusted the vaccine effectiveness in well-matched seasons for that observed in mismatched seasons (in which little or no vaccine effect should be seen due to mismatch of the influenza type with vaccine), they found little evidence of increased vaccine effectiveness in well-matched years among US Medicare patients receiving hemodialysis [68].

One study explored whether CKD affects vaccine effectiveness among older people with diabetes [63]. The "healthy vaccinee" effect was adjusted for by dividing vaccine effectiveness in winter by that observed in summer. It found a modestly protective effect of influenza vaccination against LRTI (7%, 95% CI 3–12) with no evidence of variation in vaccine effectiveness according to CKD stage. This may be an underestimate for patients with CKD, as vaccine effectiveness diminishes with age and the outcome was not specific to influenza. Given the high morbidity and mortality associated with influenza and secondary pneumonia among patients with CKD, even a low vaccine effectiveness would support vaccination.

KDIGO guidelines recommend that all adults with CKD are offered annual vaccination with influenza vaccine unless contraindicated due to allergy to seasonal influenza vaccine [1]. Live-attenuated influenza vaccination has not been tested in patients with CKD [69]. UK guidelines recommend offering inactivated influenza vaccination to adults with CKD stages 3–5, chronic kidney failure, or nephrotic syndrome, with recommendations for children varying according to age [58].

Hepatitis B

Guidelines for hepatitis B vaccination among patients with CKD have aimed to anticipate the risk of infection from dialysis [70]. Hepatitis B prevalence among patients receiving hemodialysis ranges from 1.1% to 6.1%, and patients who develop hepatitis B while receiving dialysis are more likely to become chronic carriers [70]. Vaccinating patients with CKD stages 3–4 achieves better seroconversion than vaccinating at initiation of hemodialysis [71–73]. Early vaccination may be of additional benefit to patients with diabetic nephropathy who may be at risk through blood glucose monitoring [74]. Most research into hepatitis B vaccination describes effectiveness at seroconversion as a surrogate for protection against hepatitis B infection [70].

A 2004 Cochrane review identified seven randomized clinical trials of hepatitis B vaccine effectiveness among patients with kidney failure [70]. The review found that plasma hepatitis B vaccines are safe and effective at generating protective antibody levels among patients receiving dialysis. The two trials among patients with predialysis CKD found no evidence of a difference in seroconversion following recombinant or plasma vaccine (risk ratio [RR] 0.65, 95% CI 0.28–1.53) [75, 76].

Seroconversion is lower among patients with CKD than the general population [25, 59]. Systematic reviews have found a short-term improvement in seroconversion with intradermal (rather than intramuscular) delivery and no evidence of additional benefit from "double dose" hepatitis B vaccination compared to standard doses [77, 78]. A randomized trial of 165 patients with CKD or receiving hemodialysis compared 20 μg Fendrix to double doses (2 × 20 μg HBsAg) of Engerix vaccine [79]. Fendrix is adjuvanted by monophosophoryl lipid A and adsorbed onto aluminum phosphate. Patients who received Fendrix had higher levels of seroconversion, with faster onset and longer duration of protective antibody levels. There was a higher incidence of pain at the injection site with Fendrix, but no evidence of any difference in serious adverse events. Other adjuvants that have shown promise among patients with kidney disease are levamisole [80], granulocyte macrophage colony-stimulating factor (GM-CSF) [25], and a toll-like receptor 9 agonist [81]. There may be scope to improve hepatitis B immunity for patients with CKD through further research into the optimal vaccine dose, type, route, and schedule.

KDIGO guidelines recommend vaccination for adults with eGFR < 30 ml/min/1.73m^2 and at high risk of progression of CKD, with serological testing to confirm response [1]. UK guidelines recommend vaccinating patients with CKD as soon as it is anticipated they may require dialysis or kidney transplantation, using Fendrix if they are ≥15 years old, testing antibody levels annually, and providing a booster dose for patients with antibodies below 10 mIU/ml [58].

Zoster

CKD increases the risk of herpes zoster, and the CKD patient population also has a high prevalence of diabetes and older age, both of which are risk factors for herpes zoster [82–84]. Herpes zoster may worsen kidney outcomes for patients with CKD [83]. However, older people in

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Medicare are less likely to receive herpes zoster vaccination if they have CKD than if they do not [85].

A large observational study of herpes zoster vaccination among Medicare recipients aged ≥65 years found an adjusted vaccine effectiveness of 49% (95% CI 36–56) among people with CKD and 46% (95% CI 9–68) among people with both CKD and diabetes, both similar to that among the general population of older people (vaccine effectiveness 48%, 95% CI 39–56) [82]. Small studies of varicella zoster vaccination among children with kidney disease observed high seroconversion following a second dose (>98%) and antibodies persisting over 3 years [86–88].

Varicella zoster vaccination is part of the routine childhood vaccination schedule in the United States, while the UK vaccinates older people against herpes zoster [58]. Among patients with CKD, who are at greater risk of severe disease than the general population, vaccination may have greater benefits [82]. As both varicella and herpes zoster vaccination use live attenuated virus vaccines, care must be taken to note contraindicating immunosuppression, and susceptibility and eligibility for varicella or herpes zoster vaccination should be considered in advance of immunosuppression for potential kidney transplant candidates [58].

Routine Childhood Vaccinations

In general, children with CKD are at increased risk for vaccine-preventable diseases and should receive all the routinely recommended childhood immunizations as far as possible; however, vaccination is too often delayed or overlooked [89]. Immunosuppression should be considered before delivering live or live-attenuated vaccines (including rotavirus vaccine, varicella zoster vaccine, measles, mumps, and rubella vaccine, and the live-attenuated influenza vaccine). For children with CKD, KDIGO guidelines recommend pediatric immunization schedules should be followed according to official international and regional recommendations [1]. Routine childhood vaccination schedules vary by country and are frequently updated, and so up-to-date guidance should be consulted.

Live Vaccines

Live or live-attenuated vaccines include rotavirus vaccine, varicella, and herpes zoster vaccines, measles, mumps, and rubella vaccine, yellow fever, and the live-attenuated influenza vaccine. Patients with CKD may be receiving immunosuppressive medication or have underlying or comorbid conditions that result in immunosuppression. KDIGO guidelines recommend consideration of live vaccine should include an appreciation of the patient's immune status and follow recommendations from official or governmental bodies [1]. In the United States, the Centers for Disease Control and Prevention advises that the majority of people with CKD, of any stage, have sufficient immune function to receive all live vaccines for which an inactivated vaccine is not an alternative [69].

Vaccination: Summary

In general, patients with CKD are at greater risk of infection and complications from infection. In addition to routine vaccinations, influenza, pneumococcal, hepatitis B, and zoster vaccinations should be considered. Immunosuppression must be considered before delivering live or live-attenuated vaccines, but most patients with CKD may safely receive all live vaccines for which an inactivated vaccine is not available [69].

Vaccination is a vital but under-used tool among patients with CKD [85, 89]. Although it is true that vaccine response can be diminished in CKD compared to the general population, vaccines prevent infections and improve outcomes. Indeed, given the higher risk of vaccine-preventable infection and poorer outcomes of infection associated with CKD, vaccinations are particularly important among this high-risk population.

Treating Infections in CKD

Considering the poor outcomes of infections in those with CKD, it is imperative that infections are treated promptly but appropriately to achieve maximum effect. Patients with CKD are not only subject to infection, but, if inappropriately managed, may plausibly become hosts of antibiotic-resistant pathogens, increasing the treatment difficulty. Higher rates of infection in patients with CKD result in more frequent use of antibiotics [90] and more frequent hospitalization [2, 5, 9], which increases their exposure to microbes including multidrug resistant organisms (MDROs) [91]. A recent study from China indicated the odds of infections by MDROs was 19% and 41% higher in those with eGFR between 30 and 60 ml/min/1.73m^2 and eGFR < 30 ml/min/1.73 m^2, respectively, compared to those with eGFR 60–104 ml/min/1.73m^2 [92].

It is important that treatment does not cause pathogen drug resistance and therefore treatment should be rationalized whenever possible; this means, for example, that self-limiting infections should not be treated with antibiotics. For patients with CKD, vigilance is required and they need to be told at which point they should come back to seek further help and care should their condition worsen, so there is no delay with treatment should it become necessary. The way that patients initially presented and what they were told should be diligently documented so any other healthcare provider will be able to assess whether patients have improved or worsened.

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When it comes to actual prescribing of antimicrobial drugs when the infection is deemed to require treatment, it will depend on the health system and the local circumstances as to which drug is chosen. For example, many health systems have ongoing monitoring systems of local antibiotic resistance of key pathogens, with resulting antibiotic treatment handbooks that recommend a particular first-line treatment when a person presents with a particular infection. Antimicrobial stewardship means that whenever possible there should be cultures taken so that treatment can be narrowed down once the pathogen has been identified, to enhance treatment success while minimizing further development of antibiotic resistance. Depending on the health system, some pathogens may need to be notified to central authorities, and infections and treatments given will be monitored. For example, in many hospitals in the UK methicillin-resistant staphylococcal infections are part of quality monitoring, with internal targets. If targets are not met, the hospital's infection control staff will retrain the unit and review infection control policies (e.g. decolonization regimes, swabbing/culturing every patient, etc.) to prevent such infections occurring. Monitoring of infections, treatments given, and outcomes are simpler if electronic health records are used, as this allows standardized centralized analysis. These are all general points of infection control policies that have general value irrespective of CKD status, but the stakes of patient management and antimicrobial stewardship are raised by the higher rate of infection with MDROs among patients with CKD.

Prescribing Antibiotics in CKD

If a patient with CKD requires antibiotics with a drug that is partially or fully renally cleared, dosing must take the patient's impaired kidney function into consideration. How this is approached depends on how the drug acts on the infection (i.e. pharmacodynamics). For drugs that act immediately on the pathogen with an effect dependent on concentration (e.g. aminoglycosides), the dosing interval should be increased. For drugs that require a constant level to be maintained over a prolonged time to eliminate the pathogen (e.g. beta-lactams), patients should be given smaller doses in the normally recommended dosing interval. For some infections, an antimicrobial which is not renally cleared may be an alternative.

In practice, it can be challenging to adjust interval or dose correctly, as this requires an estimate of the underlying kidney function. Especially in the context of AKI, it is very difficult to know what the true kidney function is. Estimating kidney function using the most recent test results before onset of infection will tend to overestimate kidney function during the infection. This is not ideal, but will ensure that a sufficient dose of antibiotic is given to treat the infection effectively, without delay. The dose and interval should then be reviewed once more current test results are available. Estimation should be using the best validated eGFR formula for a given patient, taking into account their body surface area (BSA). The standard eGFR is for a BSA of $1.73m^2$, hence, for the individual the GFR is:

$$GFR = eGFR * BSA / 1.73m^2$$

There are further formulas that can be used to adapt the drug dose as AKI improves or worsens [93]. Ideally, doses should be adapted following measurement of drug levels of nephrotoxic drugs to minimize toxicity and to maximize therapeutic effects, especially if there is prolonged treatment, as, for example, for tuberculosis [94]. At the time of writing, several recent reviews have discussed these issues in more detail and provide dose adjustment tables for a range of antimicrobials [95–97], but this is an area of ongoing research and guidance is evolving rapidly.

Many patients with CKD or AKI will not be managed by nephrologists, and therefore it is important to consider the surrounding health system to understand how treatment and infection outcomes in CKD can be improved. Unsurprisingly, dosing errors and inappropriate prescribing for CKD stage are common in routine practice. Electronic prescribing software has the potential to reduce such errors by identifying CKD through diagnosis or laboratory results, suggesting point of care testing, recommending preferred antimicrobials and dose, and alerting prescribers to drug interactions or kidney dysfunction in the presence of a renally cleared drug. This has been rolled out in settings from hospitals to community pharmacies with varying success [98, 99]. Safely implementing computer-decision support for medication is not straightforward, and outcomes should be monitored. Suboptimal design, alert fatigue, workarounds, and lack of training can result in unintended consequences, while success depends on prescribers finding the alerts valuable and acting on the information received [100].

Other Considerations

Aside from immediately treating the infection, there also should be consideration given to other medications that a patient with CKD is prescribed. This may include checking for drug interactions (taking into account the kidney function of the patient). For patients receiving long-term immunosuppressant medications, more serious or atypical infections may need to be considered as part of a differential diagnosis, and clinicians may need to consider whether there is a need for preventative antibiotics or antiviral medications (discussed in other chapters, e.g. for transplantation).

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Conclusions

CKD is a clear risk factor for developing infections, often requiring hospitalization. Hospitalization with an infection may worsen kidney function, and there is a graded increased risk of adverse outcomes including mortality. To prevent poor outcomes, patients need to be aware of these risks, to know when to seek help when they are unwell, and to receive timely and appropriate treatment of their infections. Whenever possible, patients with CKD should be vaccinated against infections to reduce future risks. Future trials of vaccination for infection should consider tailored vaccination programs that take into account the observed reduced immune response in patients with CKD.

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33

Treatment of Anemia in Chronic Kidney Disease

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Introduction

The prevalence of anemia increases as chronic kidney disease (CKD) progresses by stage. Anemia is caused by erythyropoietin deficiency, disordered iron metabolism, blood loss, infection, inflammation, and other less frequent causes.

Patients with CKD and moderate anemia maintain this Hb range for years: most patients with moderate anemia (hemoglobin [Hb] level < 11 g/dl and > = 9g/dl), nondialysis-dependent CKD, and type 2 diabetes are able to maintain a Hb level >9 g/dl (i.e. avoid severe anemia) when followed for an average of 2.3 years [1].

In the Trial to Reduce cardiovascular Events with Aranesp Therapy (TREAT), Hb declined precipitously in the year prior to the development of end-stage renal disease (ESRD) (irrespective of whether assigned to Aranesp or placebo) without biochemical evidence of iron deficiency [2]. Once ESRD occurs, severe anemia is more common and the need for blood transfusions far higher than in nondialysis CKD [3].

Nondialysis CKD and dialysis-dependent ESRD should probably be studied as two separate phases of kidney disease because of the following: (i) different trajectories for Hb levels, (ii) different hemodynamic and metabolic milieus, and (iii) changing pathogenesis of cardiac disease from predominantly atherosclerotic events to an equal prominence of cardiac failure events linked to nonatherosclerotic processes [4].

In cohort studies, anemia has been associated with the development of left ventricular hypertrophy (LVH), heart failure, cardiovascular (CV) hospitalizations, mortality, and diminished quality of life [5–7].

In the early decades of dialysis therapy blood transfusions were the mainstay of anemia therapy, but in the last three decades large clinical trials have been undertaken to determine the efficacy of erythropoiesis-stimulating agents (ESAs) [8–12], and more recently peginesatide [13–14] and intravenous iron [15]. Currently trials of novel prolyl hydroxylase inhibitors (PHI) that stabilize hypoxia inducible factor (HIF) are ongoing. Table 33.1 provides recommendations on the treatment of anemia in chronic kidney disease based on the certainly and strength of the evidence.

Clinical Outcomes in Randomized Controlled Trials

The choice of interventions to treat or prevent anemia in CKD should be influenced by the results of randomized controlled trials (RCTs). The clinical outcomes studied in RCTs include change in Hb levels, blood transfusion rates, CV events, and quality of life. In addition, adverse events need to be considered.

Change in Hb Levels

This is easy to assess, but creates problems because nephrologists tend to focus on the levels at which therapy should begin and target levels for therapy. It would be preferable to individualize therapy by determining whether patients have symptoms attributable to anemia and provide therapy to treat symptoms, rather than treat everybody based on test values.

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Table 33.1 Treatment of anemia in chronic kidney disease.

Treatment	Recommendation	Certainty of evidence: *high, weak, low, very low*	Strength of recommendation: *strong or weak*
Blood transfusions	Avoid red cell transfusions to minimize the general risks related to their use (1B)	Weak	Strong
	In patients eligible for organ transplantation avoid when possible red cell transfusions to minimize the risk of allosensitization (1C)	Low	Strong
	The benefits of red cell transfusions may outweigh the risk in patients in whom ESAs are ineffective and in patients at risk from ESA therapy (previous or current malignancy or previous stroke) (2C)	Low	Weak
	The decision to transfuse a CKD patient with nonacute anemia should not be based on any arbitrary Hb threshold, but should be determined by the occurrence of symptoms caused by anemia (2C)	Low	Weak
ESAs	(A) In initiating and maintaining ESA therapy balance the potential benefits of reducing blood transfusions and anemia-related symptoms against the harm in individual patients (e.g. stroke, vascular access loss, hypertension) (1B).	Weak	Strong
	(B) In CKD ND start ESA therapy when Hb falls below 9 g/l. BUT individualize the decision to start ESA therapy based on the rate of decrease of Hb, prior response to iron therapy, the risk of needing a blood transfusion, the risks of ESA therapy, and the presence of symptoms attributable to anemia (2C).	Low	Weak
	(C) In dialysis patients start ESA before Hb falls below 9 g/l by starting ESA therapy when the Hb is between 9 and 10 g/l (2B).	Low	Weak
	(D) In CKD ND and D target Hb should be 10–11.5 g/l (2C).	Low	Weak
	(E) ESAs should not be used to intentionally raise Hb above 13 g/l (1A).	High	Strong
	(F) Avoid ESAs in patients with active malignancy, history of solid organ malignancy, or history of stroke (2C).	Low	Weak
	(G) In patients with ESA hypo-responsiveness avoid repeated escalations in ESA dose beyond double the weight-based dose (2D).	Low	Weak
Intravenous iron	(A) For anemic adult CKD patients not on iron or ESA therapy, in whom a raise in Hb is desired, and whose TSAT is <30% and ferritin is <500 ng/ml, give a trial of IV iron (2C).	Low	Weak
	(B) For adult dialysis patients on ESA therapy, in whom a raise in Hb or reduction dose of ESA is desired, and whose TSAT is <30% and ferritin is <500 ng/ml, give a trial of IV iron (2C).	Low	Weak
	(C) In adult dialysis patients maintain TSAT between 20% and 40% and ferritin between 200 and 700 ng/ml in a proactive fashion (1B).	Weak	Strong

ESA: Erythropoiesis–stimulating agents; CKD: Chronic Kidney Disease; Hb: Hemoglobin; ND: Non Dialysis; D: Dialysis; TSAT: Transferrin saturation; IV: Intravenous.

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Blood Transfusions

Avoidance of blood transfusions is sufficiently desirable that it is currently the major reason for treatment of severe anemia (Hb < 9 g/dl).

Cardiovascular Events

Events arising from atherosclerosis of coronary, cerebral, and peripheral arteries occur frequently in CKD. As CKD progresses, LVH and cardiac failure events arising from cardiomyopathy occur more frequently [4]. The temptation is to combine both of these types of CV events, but this should be resisted because they have different pathogeneses. Assessment of CV events requires thousands of patients in RCTs. In addition, surrogate markers for CV events, such as echocardiographic measurement of LVH and left ventricular (LV) diameter and function, are often undertaken, but they do not substitute for clinical outcomes when applying the results of RCTs to clinical decision making.

Quality of Life

Quality of life has multiple domains and questionnaires exist to measure these domains, such as the SF 36 or Kidney Disease Quality of Life (KDQoL). However, anemia treatment is unlikely to influence several of the domains. Consequently, it is advisable to identify a priori prespecified outcomes potentially susceptible to anemia treatment, such as tiredness, vitality, and fatigue. A major problem concerns interpretation of results, especially as the definition of clinically significant changes in symptom scores is not based on strong clinical epidemiology science.

Harms vs. Benefits

Large trials are necessary to provide evidence on the harms:benefits ratio. For example, TREAT was undertaken nearly 20 years after the introduction of ESAs and was big enough to identify the increased risk of stroke in anemic diabetic CKD patients treated to normalize Hb levels with Aranesp [12]. Although some recommend conclusions derived from meta-analysis of all types of trials of a particular agent, sometimes more utility is derived from large RCTs designed to answer a clinical management question.

Erythropoiesis-stimulating Agents

Recombinant human erythropoietins have been used to treat anemia for up to three decades. During the past decade, ESA doses have declined following publication of RCTs demonstrating harm when the target Hb for ESA treatment was normalization of Hb [16]. As a result of these trials, the target Hb is between 10 and 12 g/l. A critical appraisal of these RCTs follows [17].

Treatment of Severe Anemia

There are no large RCTs of ESA therapy in patients with severe anemia (baseline Hb <9 g/dl) in which clinical endpoints and safety were assessed. In 1990, the Canadian Erythropoietin Study Group reported an RCT in which ESA was utilized in 110 hemodialysis patients with Hb levels below 9 g/dl, and three randomly allocated groups were followed (placebo, low target Hb 9.5–11 g/dl, high target Hb >11 g/dl). Baseline Hb was 7.0 g/dl and transfusion requirement was seven transfusions per year. After 8 weeks, 58% ($n = 23/40$) in the placebo group were transfused and only 3% ($n = 1/40$) in the low Hb group. After 6 months, clinically important improvements in fatigue, physical function, and 6-minute walking tests were reported for the low Hb group compared with the placebo group, but no improvement was observed when comparing the low and high Hb groups. A strategy to treat CKD patients with ESAs when Hb falls below 9 g/dl seems justified on the grounds of reduction in transfusions and improvement in quality of life, despite the lack of data on safety.

Treatment of Moderate Anemia

There are several large RCTs of ESA therapy in which baseline Hb was higher than 10 g/dl [8–12]. The intervention being tested in these trials was correction of anemia with ESAs, compared with partial correction of anemia with ESAs in four RCTs [8–11] and with placebo in one [12].

Normal Hematocrit Study

Prevalent hemodialysis patients with symptomatic cardiac disease (congestive heart failure or ischemic heart disease) ($n = 1233$) were enrolled in this RCT [8]. In the normal hematocrit group treated with epoetin, there were 183 deaths and 19 myocardial infarcts, producing 202 primary events, compared with 164 events (150 deaths and 14 myocardial infarcts) in the group in which anemia was partially corrected with epoetin. Although the primary event rate was significantly different ($P = 0.03$), the hazard ratio (HR) was 1.3, with 95% confidence intervals (CIs) being 0.9–1.9, following correction for previous interim analyses. The trial was stopped early, not because of these somewhat equivocal results, but because the intervention being tested was certainly causing harm in a situation wherein the primary hypothesis was unlikely to be proven: 39% had vascular access clotting in the intervention arm and 29% in the control arm ($P = 0.001$).

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Canada–Europe Study

Incident hemodialysis patients without symptomatic cardiac disease (congestive heart failure or ischemic heart disease) were enrolled in this RCT [9]. A similar number of patients (n = 596) were enrolled in this study as in the Cardiovascular Risk reduction in Early Anemia Treatment with Epoetin (CREATE) study (see next section) (n = 603), but the primary outcome was not clinical events, but rather change in LV volume index and LV mass index. The change in both indices was similar in the correction of anemia group and in the partial correction group. Nonetheless, important clinical observations were made. A safety signal was observed as 12 neurological events occurred in the high Hb group (13.5–14.5 g/dl target) and four in the low Hb group (9.5–11.5 g/dl target) ($P < 0.05$), a signal confirmed by TREAT (see below) [8]. As one might expect, the high Hb group received significantly fewer transfusions than the low Hb group, but the extent of the benefit was modest: although 9% in the high Hb arm received a transfusion compared with 19% in the low Hb arm (P = 0.004) during the 2-year study, the number of transfusions per patient per year was 0.3 in the high Hb arm and 0.7 in the low Hb arm ($P < 0.0001$) [18].

Cardiovascular Risk Reduction in Early Anemia Treatment with Epoetin study

Predialysis CKD patients (n = 603) with mean estimated glomerular filtration rate (eGFR) equal to 24 ml/min were enrolled in this RCT [10]. Baseline Hb was 11.0–12.5 g/dl. Normalization of Hb with epoetin was compared with late partial treatment of Hb (i.e. when Hb fell below 10.5 g/dl, to a target of 10.5–11.5 g/dl). The trial was underpowered for the primary outcome, a composite of eight CV events. Dialysis was required in significantly more patients in the high Hb group than in the low Hb group, but this may have resulted from the open-label design of the study in which symptoms might have been attributed to uremia with the knowledge that they were not attributable to anemia. This interpretation is supported by the fact that the rate of fall of eGFR in the two groups during the 3-year study was similar and by the results of TREAT, in which renal outcomes were the same in the placebo and high Hb groups [12].

Correction of Hemoglobin and Outcomes in Renal Insufficiency

This RCT was undertaken in 1432 predialysis CKD patients, half of whom had diabetic renal disease; baseline creatinine clearance was 37 ml/min [11]. Withdrawal rate was high: 17% due to renal transplantation and 21% for other reasons. The trial was stopped prematurely at a time when the primary endpoint (death or composite CV event) occurred significantly more often in the high Hb group compared with the low Hb group (P = 0.03). However, there were differences in baseline CV comorbidity such that, when taken into account in multivariate models, the hazard associated with high Hb was no longer statistically significant (P = 0.11) [14]. The conclusion that correction of anemia with erythropoietin is not associated with increased CV events is supported by the results of TREAT [12] in which CV outcomes were the same in the placebo and high Hb groups.

Trial to Reduce Cardiovascular Events with Aransep Therapy

This trial in diabetic patients with moderate anemia is by far the biggest RCT of ESA therapy performed (n = 4038) and had the best research design, as it was placebo-controlled and double-blind [12]. In the intervention arm darbepoetin (Aranesp) was used to achieve Hb higher than 13 g/dl, and in the placebo arm rescue therapy with darbepoetin was undertaken when Hb fell below 9 g/dl and placebo was restarted when Hb was higher than 9 g/dl. Baseline eGFR was 34 ml/min and baseline Hb was 10.4 g/dl. Median follow-up was 29 months, equivalent to 9941 patient-years. Median Hb in the high Hb arm was 12.6 g/dl and in the low Hb arm it was 10.6 g/dl. There were no differences in CV or renal outcomes comparing the two groups. The HR for death/composite CV events was 1.05 (95% CI 0.94–1.17) and for death or ESRD it was 1.06 (95% CI 0.95–1.19). However, there was a substantial increased risk of stroke (HR 1.92, 95% CI 1.38–2.68), although the risk of stroke attributable to the high Hb intervention was relatively small: 5.0% of the high Hb group had a stroke compared with 2.6% in the placebo group. The attributable risk of stroke in those with a prior history of stroke was substantially higher. Venous thromboembolic events occurred significantly more frequently in the high Hb arm (2%) compared with 1.1% in the placebo arm (P = 0.02). A signal that normalization of Hb with darbepoetin may be harmful in patients with a history of malignancy was reported following a post hoc analysis: 14 of 188 (7.4%) patients with a baseline history of malignancy died from cancer in the darbepoetin arm compared with 1 of 160 (0.6%) in the placebo arm (P = 0.002). Red blood cell transfusions were prescribed surprisingly frequently, and more often in the placebo arm (25%) compared with the high Hb arm (15%).

Hyporesponsiveness

A report from TREAT assessed the initial Hb response to darbepoetin (Aranesp) after two weight-based doses at 2-weekly intervals in 1842 diabetic patients with CKD [19]. Patients with a poor response, the lowest quartile who had

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less than 2% change in Hb level after 1 month, had higher rates of the composite CV events (adjusted HR 1.31, 95% CI 1.09–1.59) or death (adjusted HR 1.41, 95% CI 1.12–1.78) compared with those with a better response. Although this differential effect may be related to comorbidity in hyporesponsive patients, nonetheless it is possible that high ESA doses in hyporesponsive patients may be toxic.

Meta-analyses

Palmer et al. [20] concluded that higher Hb levels in CKD increase risk for stroke (relative risk [RR] 1.51, 95% CI 1.03–2.21), hypertension, and vascular access thrombosis (RR 1.33, 95% CI 1.16–1.53), and probably increase risk for death (RR 1.09, 95% CI 0.99–1.2), serious CV events (RR 1.15, 95% CI 0.98–1.33), or ESRD (RR 1.08, 95% CI 0.97–1.20).

In 2014, a Cochrane review concluded that darbepoetin alfa effectively reduced blood transfusions in adults with CKD stages 3–5, but had little or no effect on mortality [21]. Its effects in adults with CKD stage 5D, kidney transplant recipients, and children with CKD remain uncertain. Another Cochrane review concluded there is currently insufficient evidence to suggest the superiority of any ESA formulation based on available safety and efficacy data [22]. A third Cochrane review concluded that continuous erythropoiesis receptor activator (a new class of third generation ESAs) had little or no effect on patient-centered outcomes compared with placebo, epoetin alfa or beta, or darbepoetin alfa for adults with CKD [23].

A meta-analysis of the effect of ESAs on health-related quality of life (HRQOL) concluded that ESA treatment of anemia to obtain higher Hb targets does not result in important differences (24), despite significant benefits being reported from the Canadian-Europe study [25], CREATE [10], and TREAT [12]. However, there may be a misinterpretation of the importance of the results, particularly if viewed through the lens of requiring a large improvement in symptom scores to be "clinically significant." In TREAT, linear repeated measure models of fatigue incorporated all symptom scores through 97 weeks, together with several baseline and interim predictors of long-term changes in HRQOL. Allocation to the placebo group was similar in magnitude to the effects of having pulmonary disease or CV disease, suggesting that these "modest" changes and fatigue scores were actually clinically important [26].

Peginesatide

Peginesatide is a dimeric pegylated peptide erythropoietic agent which was evaluated in two RCTs published in 2013 [13, 14]. The number of patients allocated to peginesatide in nondialysis CKD was 328 and in dialysis patients it was 1066. As a result of these RCTs, the FDA approved peginesatide for use in dialysis patients, but given the increased risk of CV events in nondialysis CKD patient trials, the FDA did not approve the agent for use in that group of patients.

On 23 February 2013, shortly after publication of the two trials, Affymax and Takeda, the producers of peginesatide, announced a nationwide voluntary recall of all lots of peginesatide injection as a result of new post-marketing reports of serious hypersensitivity reactions, including life-threatening or fatal anaphylaxis [27]. The rate of hypersensitivity reactions reported was 0.2%, of which approximately one-third were serious in nature. A safety signal for hypersensitivity reactions was not reported in the two *NEJM* articles, which supports the belief that these noninferiority studies were too small to provide adequate data for safety.

Intravenous Iron

During the past 6 years, use of intravenous iron has increased following the recommendation by Kidney Disease Improving Global Outcomes (KDIGO) guidelines that iron repletion should be a component of anemia management in CKD [28].

Meta-analysis comparing intravenous versus oral iron supplementation revealed that patients with CKD stages 3–5 were more likely to reach an Hb response >1 g/dl with intravenous iron (risk ratio 1.61, 95% CI 1.39–1.87) and that dialysis patients were even more likely to achieve this response (risk ratio 7.71, 95% CI 1.74–7.94) [29]. Another meta-analysis concluded that significant reductions in ESA dosing may be achieved by iron repletion in the hemodialysis population, and suboptimal iron use may require higher ESA dosing to manage anemia [30]. Nonetheless there were concerns about the safety of increased use of intravenous iron.

Recently, in a multicenter, open-label trial with blinded end-point evaluation, adults undergoing maintenance hemodialysis were randomly assigned to receive either high-dose iron sucrose administered intravenously in a proactive fashion (400 mg monthly, unless the ferritin concentration was >700 μg/l or the transferrin saturation was ≥40%) or low-dose iron sucrose administered intravenously in a reactive fashion (0–400 mg monthly, with a ferritin concentration of <200 μg/l or a transferrin saturation of <20% being a trigger for iron administration) [15]. The primary end point was the composite of nonfatal myocardial infarction, nonfatal stroke, hospitalization for heart failure, or death, assessed in a time-to-first-event analysis.

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A total of 2141 patients underwent randomization. The median follow-up was 2.1 years. Patients in the high-dose group received a median monthly iron dose of 264 mg (interquartile range [25th to 75th percentile] 200–336), as compared with 145 mg (interquartile range 100–190) in the low-dose group. The median monthly dose of an ESA was 29 757 IU in the high-dose group and 38 805 IU in the low-dose group (median difference −7539 IU, 95% CI −9485 to −5582). A total of 333 patients (30.5%) in the high-dose group had a primary end-point event, as compared with 343 (32.7%) in the low-dose group (HR 0.88, 95% CI 0.76–1.03, $P<0.001$ for noninferiority). In an analysis that used recurrent-events approach, there were 456 events in the high-dose group and 538 in the low-dose group (rate ratio 0.78, 95% CI 0.66–0.92). The infection rate was the same in the two groups.

These data support an iron repletion high-dose regimen administered proactively rather than a lower-dose reactive regimen.

Prolyl Hydroxylase Inhibitors

HIF is the major transcription factor for the erythropoietin gene. Molecules were created that inhibit the HIF prolyl hydroxylase enzyme, preventing degradation of HIF and thus upregulating the erythropoietin gene. In adults, about 90% of erythropoietin is produced by the kidneys but 10% is produced by the liver. Liver production can respond to prolyl hydroxylase inhibition by producing more endogenous erythropoietin. However, there are many other hypoxia-sensitive genes for which HIF is a key regulatory protein, including angiogenic factors. Consequently, long-term safety is a concern.

Prolyl hydroxylase inhibition (PHI) agents are oral drugs, four of which are already in stage 3 RCTs. They have demonstrated that they can raise and maintain Hb levels in a predictable and controlled manner, while enhancing iron mobilization in patients with nondialysis CKD [31–33].

Roxadustat is being studied in four RCTs in nondialysis CKD comprising 4750 patients, with one RCT comprising 2700 patients and having a primary outcome for major CV events. The same drug is under investigation in 4508 dialysis patients, with one RCT comprising 2100 patients and having a primary outcome for major CV events. Vadadustat is under investigation in 3100 nondialysis CKD patients in two RCTs and in 2600 dialysis patients in two RCTs. Daprodustat is being studied in an RCT of 4500 nondialysis patients, in another of 3000 dialysis patients, and in a third of 300 incident dialysis patients. The fourth drug is Molidustat. The results from these trials will be published during the next 3 years.

Conclusion

Current management of anemia in CKD usually combines use of ESAs and iron repletion, and is driven by the need to avoid both [1] severe anemia and the higher risk of blood transfusions, and [2] normal hemoglobin levels, which were associated with increased CV risk in ESA trials.

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Dyslipidemia in Chronic Kidney Disease

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Introduction

Cardiovascular (CV)-related mortality is the leading cause of death in patients with chronic kidney disease (CKD) [1]. However, dyslipidemia and treatment of lipids in CKD are distinct from that of the general population. A deeper understanding of how lipids behave in CKD and the results of trial data regarding CKD outcomes or lipid-lowering therapy in CKD patients are needed in order to understand how to properly treat patients with CKD. In this chapter, we will review lipid metabolism, describe changes in lipid particles and metabolism as CKD progresses, the role of these markers in CKD, and the impact of dyslipidemia and treatment with lipid-altering therapies across different stages of CKD.

Dyslipidemia Diagnosis

The Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) [2] provides a description of dyslipidemia in patients. Dyslipidemia may be defined by a total cholesterol (TC) ≥200 mg/dl, low-density lipoprotein cholesterol (LDLc) ≥100 mg/dl, high-density lipoprotein cholesterol (HDLc) <40 mg/dl, and triglycerides (TG) ≥150 mg/dl. These lipid measurements are typically used in conjunction with other comorbid measures to ascertain the 10-year risk of a CV event to evaluate indication of treatment for dyslipidemia. As will be discussed below, alterations in lipid levels across progressing CKD may alter these threshold definitions of dyslipidemia in CKD patients, and the prognosis of dyslipidemia for CV and mortality outcomes may shift as CKD progresses. However, according to the most recent American College of Cardiology and American Heart Association (ACC/AHA) guidelines [3], presence of CKD is considered a coronary risk equivalent and is itself an indication for treatment. Therefore, in patients with CKD, measuring lipid levels may be more useful to determine adherence and response to therapy, rather than as a measure to ascertain disease risk and indicate treatment.

Epidemiology

In the general population, TC, LDLc, and TG are strongly and positively associated with incident CV events [4–6], while HDLc has been associated with a lower risk of CV events. However, reverse associations between these lipid markers and CV events have been described in segments of CKD patients, a so-called "reverse epidemiology."

In nondialysis dependent chronic kidney disease (NDD-CKD), the value of lipid levels in predicting cardiovascular disease (CVD) appeared to attenuate across worsening stages of CKD, although some studies showed conflicting results. Tonelli et al. studied 836 060 adults, including 47 092 NDD-CKD patients (estimated glomerular filtration rate [eGFR] 15–59 ml/min/1.73m^2) from the Alberta Kidney Disease Network and found that the association between higher LDLc and risk of myocardial infarction (MI) was weaker for people with lower baseline eGFR despite that group having a higher absolute risk of MI [7]. Bowe et al.

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similarly found an interaction between eGFR category and HDLc for mortality risk where lower eGFR attenuated the lower risk conferred by intermediate HDLc for risk of death in a very large male cohort of US veterans [8]. The study also found a u-shaped association between HDLc and mortality risk across all eGFR groups, where higher mortality risk was observed for patients with HDLc >50 mg/dl. Moreover, Navaneethan et al. further examined HDLc mortality associations in NDD-CKD US veteran patients and reported that HDLc >60 mg/dl was associated with lower all-cause, CV, malignancy-related, and non-CV/nonmalignancy-related deaths among women but not in men [9]. Navaneethan et al. also found a shallower u-shaped relationship between TG and mortality for NDD-CKD patients age 65 years and older, but a direct linear relationship in younger patients [10]. The Atherosclerosis Risk In the Communities (ARIC) study also reported an association of lipids with coronary heart disease similar to that of the general population across eGFR groups in 807 NDD-CKD patients [11]; however, the study was only powered to adjust for four demographic covariates and may have residual confounding. Conversely, another small study of 840 stage 3 and 4 NDD-CKD patients in the Modification of Diet in Renal Disease (MDRD) cohort showed that the significant association of continuous TC with all-cause mortality was attenuated with covariate adjustment, and there was no association of TG, HDLc, and non-HDLc with all-cause or CV mortality [12]. Kovesdy et al. also studied the association between all four lipids and mortality in 1012 NDD-CKD patients in a single-center veteran study and found that compared to the highest quartile of lipid levels, lower lipid levels (TC, LDLc, TG, and HDLc) were associated with higher all-cause mortality [13]. However, these associations were attenuated after adjustment for demographics and abolished after additional adjustment for markers of malnutrition and inflammation complex (or cachexia) syndrome (MICS). Furthermore, in the African American Study of Kidney Disease and Hypertension (AASK) study, higher TC was associated with the CV endpoint in non-MICS NDD-CKD patients, but not in MICS NDD-CKD patients [14].

The concept of this reverse epidemiology relationship between lipids and outcomes in CKD has been attributed to MICS. The MICS concept was introduced by Kalantar-Zadeh et al. for dialysis patients [15] and subsequently defined by a specific diagnosis description [16]. The description of the syndrome includes medical history of weight loss, anorexia, gastrointestinal symptoms, reduced activity, comorbidity, and long dialysis vintage as well as objective examination findings (decreased subcutaneous fat, muscle wasting, low body mass index [BMI], low albumin, and low total iron binding capacity). In a subsequent publication from the same group, the malnutrition-inflammation score (MIS) correlated significantly with inflammatory markers serum interleukin (IL)-6 level and C-reactive protein (CRP) level as well as with several measures of nutritional status and risk of death [17]. In patients with more severe MICS as indicated by a high CRP and low albumin, the levels of TG and other lipid markers were also significantly decreased [18].

Studies have demonstrated the impact of MICS on the relationship between lipids and mortality in dialysis patients. In a cohort of 823 incident dialysis patients, Liu et al. showed that a 40 mg/dl increment in baseline TC was associated with a lower risk of all-cause mortality overall and in the presence of inflammation/malnutrition, but a higher mortality risk in the absence of inflammation/malnutrition in models adjusted for age, race, and sex [19]. Further adjustment for traditional CV risk factors, dialysis modality, comorbidity, and inflammatory markers attenuated the inverse association but strengthened the positive association. In keeping with these findings, another study showed that in dialysis patients, lower serum TC was a significant predictor of death, but higher TC was associated with higher death risk in a subgroup of patients with serum albumin ≥4.5 g/dl [20]. In the Taiwan Renal Registry Data System, in nonatherosclerotic cardiovascular disease (non-ASCVD), both TC >250 mg/dl and <150 mg/dl were associated with a higher risk of mortality compared to the reference (TC 150–200 mg/dl); however, in the ASCVD patients, only TC <150 mg/dl had a higher risk [21]. In a cohort of hemodialysis patients, each 50 mg/dl excess in TG was associated with a progressively lower risk of all-cause and CV mortality in patients with a waist circumference <95 cm but with a progressively higher risk in patients with a waist circumference above this threshold [22].

Kilpatrick et al. also examined the association of lipid markers with mortality in consideration of MICS in a large dialysis cohort [23]. Both higher TC and LDLc showed a paradoxical association with better survival. Hyper-triglyceridemia (>200 mg/dl) also showed a similar trend. The association between a low serum LDLc (<70 mg/dl), which was prevalent among almost 50% of hemodialysis patients in the cohort, and higher all-cause death risk was robust to multivariate adjustment, including MICS markers. In subgroup analyses, these paradoxical associations persisted among most subgroups, although they tended to be stronger among hypoalbuminemic (<3.8 mg/dl) patients and those with a lower dietary protein intake (<1 g/kg/day). Conversely, in African American patients, a high serum LDLc (>100 mg/ml) was associated with a higher adjusted CV death hazard ratio. The authors of the study cautioned that the so-called reverse epidemiology observations of lipids with mortality in dialysis patients should not be considered causal or lead to the nihilistic conclusion of no clinical benefit from cholesterol lowering therapy. Another small study similarly showed lower TC

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predicted all-cause and CV mortality in hemodialysis patients [24]. Other studies in hemodialysis patients have also shown that higher TG, TG/HDLc ratio, non-HDLc, and non-HDLc/HDLc ratio were inversely associated with mortality risk in hemodialysis patients in models adjusted for markers of malnutrition and inflammation [25, 26]. In the same cohort, higher levels of HDLc [27] and increases in HDLc [28] were associated with higher mortality risk in hemodialysis patients in analysis with MICS adjustment. A further study comparing HDLc-mortality associations in East Coast versus West Coast Hispanic dialysis patients showed the relationship of higher HDLc with mortality differed according to coast and may be explained by geographical variances in racial-ethnic and genetic distinctions [29].

Associations of lipid markers with outcomes in peritoneal dialysis patients have conflicting results. In 1053 continuous ambulatory peritoneal dialysis (CAPD) patients, lower TC levels were associated with a higher risk of all-cause mortality, including in those taking or not taking lipid-modifying medications [30]. Additionally, in a cohort of 749 Korean incident peritoneal dialysis patients, lower TC, LDLc, TG, and HDLc were associated with a higher all-cause mortality risk, and lower TC and LDLc were associated with higher CV mortality risk. However, these associations may be impacted by MICS as well. In a study of nondiabetic CAPD patients, metabolic syndrome (MetS), characterized by elevated TG and lower HDLc, was a predictor of mortality in patients with serum albumin >3.0 g/dl, but not in those with albumin <3.0 g/dl [31]. Another study similarly showed that the association between MetS and mortality in peritoneal dialysis was attenuated after adjustment for CRP. One small study has shown that higher very-low-density lipoprotein cholesterol (VLDLc) was associated with higher mortality risk in peritoneal dialysis patients even after adjustment for MICS covariates [32]; however, additional studies are needed to support this different finding.

In transplanted patients, elevated levels of TC or its subfractions and elevated TG levels have not been shown to be associated with increased risk for patient mortality or allograft loss [33], possibly due to the variability of lipoprotein concentrations and of the factors affecting graft survival. Across CKD stages, the relationship of lipids with mortality and CV outcomes is paradoxical to that observed in the general population.

Dyslipidemia as a Precursor of CKD

CKD is a frequent complication of type 2 diabetes, and type 2 diabetes is the leading cause of CKD [1]. The majority of patients with type 2 diabetes also have features of MetS, including obesity, hypertension, elevated TGs, and low HDLc [2, 34]. In patients with MetS, dyslipidemia occurs due to an increased production and decreased catabolism of VLDLc, thereby resulting in an increase in the fraction of small dense low-density lipoprotein (sd-LDL) and catabolism of HDL attributable to insulin resistance (see Figure 34.1 for a basic comparison of density and lipid

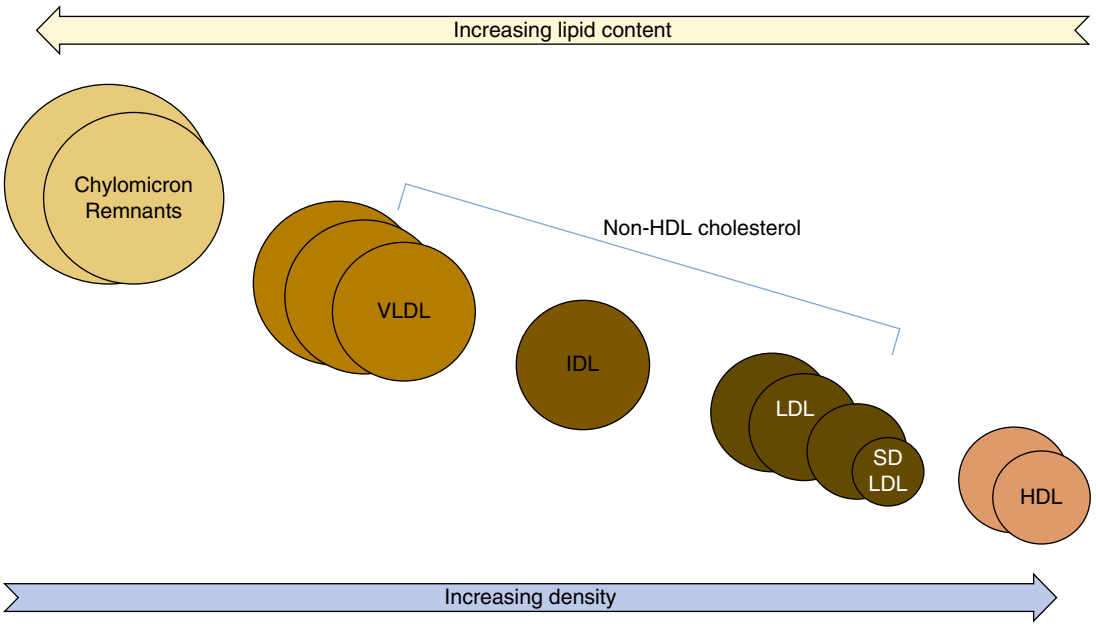

Figure 34.1 Serum lipoproteins: relative density and lipid content. HDL, high-density lipoprotein; IDL, intermediate density lipoproteins; LDL, low-density lipoprotein; SD LDL, small dense low-density lipoprotein; VLDL, very low-density lipoprotein.

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content across serum lipoproteins, and Figure 34.2 for a summary of MetS impact on VLDL).

Patients with MetS also have an increased likelihood of developing CKD [35, 36] and the strength of this association seems to increase with the number of MetS components present [37]. Both high TG and low HDLc have been independently associated with the risk of incident CKD [38]. The higher quartile of TG/HDLc ratio at baseline was significantly associated with greater decline in eGFR and increase in urinary protein excretion after adjustment for confounding factors [39, 40]. We conclude that changes in the concentration and composition of lipoproteins characteristic of MetS and type 2 diabetes predict incident CKD and consequently may be transferred to the CKD population and become a feature of CKD.

Dyslipidemia in Nonproteinuric NDD-CKD and Hemodialysis

Dyslipidemia in nonproteinuric NDD-CKD patients is characterized by the same features as dyslipidemia in MetS:

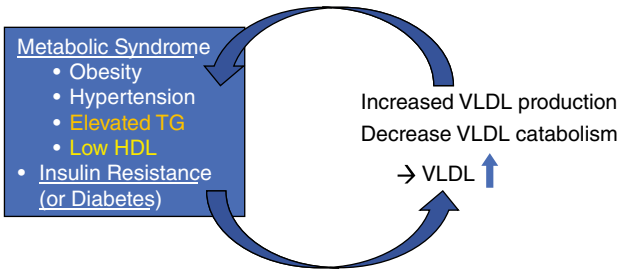

Figure 34.2 Metabolic syndrome impact on lipid metabolism. HDL, high-density lipoprotein; TG, triglycerides; VLDL, very low-density lipoprotein.

increases in TG concentration, changes in LDL subfraction distribution, and decreases in HDLc concentration.

Changes in Triglyceride-carrying Lipoprotein Particles in NDD-CKD

Similar to MetS, dyslipidemia of CKD patients without significant proteinuria is characterized by hypertriglyceridemia, elevated plasma levels of VLDLc, intermediate density lipoprotein (IDL), and chylomicron remnants (Figure 34.1), and additionally low plasma HDLc and its main apolipoprotein (Apo), ApoA-I [41]. While in MetS the primary cause of hypertriglyceridemia is an increased production of VLDL TGs attributable to the increased flow of free fatty acids [42, 43], in NDD-CKD without proteinuria a decreased VLDL metabolism appears to be the main cause [44, 45].

The average TG concentration increases with CKD stage and an inverse association between eGFR and TGs was described [10, 46–48]. The pathophysiology of the defect in TG metabolism in CKD is attributable primarily to an increase in ApoC-III resulting in a decreased catabolic rate of VLDL and IDL [49], with ApoC-III concentration as the only independent predictor of clearance defects (Figure 34.3). On VLDL particles, ApoC-III is an inhibitor of lipoprotein lipase (LPL) activity responsible for VLDL catabolism. In CKD, the ApoC-III fractional catabolic rate is also decreased [50], leading to the increase in its concentration.

The decreased TG removal in CKD is also in part attributable to a decrease in LPL function, although the contribution is not as high as that of ApoC-III [51]. In addition, hypertriglyceridemia of nonproteinuric NDD-CKD is mainly attributable to a lipolytic defect due to a progressive increase in ApoC-III as CKD progresses.

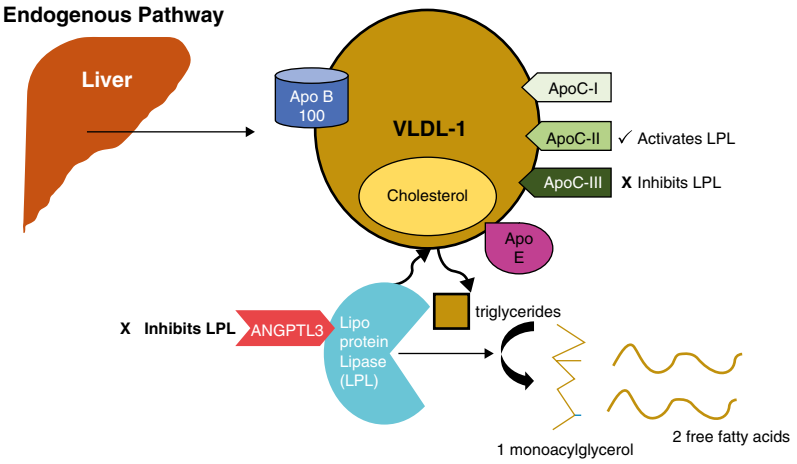

Figure 34.3 Endogenous pathway of VLDL metabolism. ANGPTL3, angiopoietin-like protein 3; APO, apolipoprotein; LPL, lipoprotein lipase; VLDL, very low-density lipoprotein.

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Changes in Triglyceride-carrying Lipoprotein Particles Common to NDD-CKD and Hemodialysis

Additional pathophysiological mechanisms leading to dyslipidemia have been described in hemodialysis patients, although it is not clear to what extent these mechanisms also operate in earlier stages of CKD. In hemodialysis patients, concentrations of VLDLc ApoC-II/C-III ratio were lower (attributed to higher ApoC-III concentrations) even in the presence of normal TG [52]. In addition, studies described the presence of an inhibitor of LPL in the plasma of hemodialysis patients [53, 54]. Another contributor to hemodialysis-related changes in LPL is the progressive decrease in the presence of an activating factor for LPL in the HDL fraction of the serum [55]. Hemodialysis patients also have a defect in the removal of chylomicron remnants [56, 57], resulting in a prolonged circulation time. These studies could be interpreted as a severe defect in postprandial lipoprotein metabolism, specifically a decrease in remnant uptake by the liver, in hemodialysis patients. Other studies have shown that the function of lipases is reduced by increased levels of the angiopoietin-like protein 3 (ANGPTL3) and 4 which is markedly increased in hemodialysis [58, 59]. LPL level seems to decrease with dialysis duration [60], indicating a time effect on the lipolytic deficiency. The use of heparin (which detaches LPL from the endothelium and releases it into the circulation) in hemodialysis has an additional impact on atherogenicity [61]. After a hemodialytic procedure with heparin, readily available LPL in circulation readily metabolizes VLDL, resulting in a significant reduction of TG concentration and an increase in VLDL atherogenic remnants. The authors interpreted their data as showing that heparin administration during hemodialysis leads to a massive production in atherogenic particles because of the acute stimulation of LPL activity not followed by an efficient removal of lipoprotein remnants.

Changes in LDL Common to Nonproteinuric NDD-CKD and Hemodialysis

Although LDLc concentrations in nonproteinuric CKD patients are similar to those of normal controls, there are important differences in LDL kinetics in nonproteinuric CKD and hemodialysis patients as compared to control patients. The fractional clearance rate of LDL is markedly diminished and possibly decreases with the decrease in eGFR [62]. However, since LDL and IDL levels are regulated by both clearance as well as production, there is no clear relationship between clearance and concentration [63].

Since the majority of patients with nonproteinuric CKD and hemodialysis have hypertriglyceridemia, the spectrum of LDL particles is shifted toward smaller and denser particles [64, 65]. As with TG concentrations, sd-LDL is significantly associated with CKD stage and BMI [66]. In hemodialysis patients, even in normotriglyceridemic patients, there are changes in the composition of lipoproteins indicating a shift toward denser subfractions in the absence of hypertriglyceridemia [67], while in hypertriglyceridemia there is an increase in particle number indicating increased atherogenicity for the same amount of LDL cholesterol [68].

Increased oxidative stress is a major contributor to the increased atherosclerosis and CV morbidity and mortality found in uremia [69]. In different stages of CKD there is a marked increase in oxidized LDL [70] or of antibodies against oxidized LDL [71].

Another characteristic of LDL spectrum lipoproteins in CKD is an increased concentration of lipoprotein (a) (Lp(a)), a lipoprotein subclass associated with atherogenic risk. Lp(a) levels have been found to be elevated across the entire spectrum of eGFR in CKD patients [72]; kidney function was inversely correlated with Lp(a) levels, but this relationship is present only in nonproteinuric CKD and for subjects with large Apo(a) isomorphs [73]. The increase in Lp(a) concentration in CKD is attributable to a decreased removal rate [74]. Elevated Lp(a) is associated with a more rapid eGFR decline [75].

Dyslipidemia in Nephrotic Syndrome and Peritoneal Dialysis

In nephrotic syndrome and peritoneal dialysis, additional pathophysiological mechanisms are added to those described for nonproteinuric CKD and hemodialysis.

Nephrotic Syndrome

Early studies described an increase in the production of lipoproteins in nephrotic syndrome in proportion with albuminuria [76–78]. However, this conclusion was questioned when an improved technology was used [79] and showed that VLDL Apo B100 levels were primarily increased as a consequence of a decrease in fractional catabolic rate. However, LDL Apo B100 synthesis rate was significantly increased in nephrotic patients compared to controls and was greater than that of VLDL Apo B100 in some patients, suggesting that LDL may be, in part, derived from a direct secretory pathway. These data indicate that increased VLDL in nephrotic patients results from a decreased catabolism, while increased LDL results from increased synthesis. However, patients with nephrotic syndrome with no

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hypertriglyceridemia have low fractional catabolic rates of LDL Apo B and no overproduction of LDL Apo B [80]. A receptor mediated uptake of LDL defect plays an important role in regulating LDL Apo B concentration [81].

Patients with nephrotic syndrome were shown to display VLDL enriched with cholesteryl esters (CE), with a CE/TG ratio approximately twice that of controls and plasma cholesteryl ester transport protein (CETP) concentration significantly increased compared to controls. CETP is involved in HDL/VLDL metabolism and mediates the transfer of CE in HDL to VLDL in exchange for TGs. Treatment with corticosteroids or angiotensin receptor blockers reduced proteinuria and LDLc and normalized plasma CETP [82–84]. The drop in CETP correlated with the decrease in LDLc

Other authors identified a role for elevated proprotein convertase subtilisin/kexin type 9 (PCSK9) in the hyperlipidemia of nephrotic syndrome [85, 86] and PCSK9 is corrected by dialysis and normalized after renal transplant [87]. PCSK9 is an enzyme that mediates the catabolism of the LDL receptor, and thereby its inhibition results in an increased LDL receptor number. Plasma PCSK9 level is directly and strongly correlated to total and LDL cholesterol concentrations.

Peritoneal Dialysis

In 1987, Sniderman et al. showed that compared to hemodialysis patients, CAPD patients have higher TC, LDLc, TG, Apo B, LDL-ApoB, and VLDL-ApoB [88, 89]. In addition, the clearance of LDL in CAPD patients has been shown to be markedly decreased in comparison to that of control subjects [90]. Elevated levels of plasma VLDL and reduced levels of plasma HDL were maintained in these patients throughout 5 years of CAPD, whereas the initially increased LDL levels showed a tendency toward normalization [91]. All plasma lipoproteins (VLDL, IDL, LDL, and HDL) are present in the peritoneal effluent. The peritoneal protein clearance correlates positively with plasma levels of TG and LDL, and negatively with plasma HDL. In addition, an inverse correlation was observed between plasma levels of HDL and its peritoneal clearance. The continuous peritoneal loss of HDL and the hypertriglyceridemia contribute most to the persistent low plasma levels of HDL in CAPD patients.

HDL Changes in CKD

In CKD, HDL undergoes a number of structural and functional changes. Researchers have explained that these changes may explain why the relationship of HDL with outcomes in kidney disease patients changes across progressing disease [27, 28].

HDL Structural Changes

In 1966, Lewis et al. described that in anephric patients, HDL is very low, and it increases after transplantation [92]. In uremic patients, hypertriglyceridemia and low LPL (signifying a reduced lipid metabolism) are associated with higher HDLc [93]. Inflammation contributes to the reduction in HDL concentration in end-stage renal disease (ESRD) [94]. ApoA-I, the main HDL lipoprotein, changes inversely with serum concentrations of CRP and the inflammatory marker α 1 acid glycoprotein (α 1AG). Apo A-I fractional catabolic rate was 50% increased in hemodialysis patients, whereas the production rate remained unchanged [95]. Oxidized HDL is also increased in dialysis patients [96].

The protein composition of HDL is also changed, with a higher retinol-binding protein 4, serum amyloid A1, and lipoprotein-associated phospholipase A2, and lower vitronectin [97–99]. The composition changes also correlate with the observed impaired ability of uremic HDL to promote cholesterol efflux from macrophages.

Another characteristic change in HDL composition in CKD, but not in nephrotic syndrome, is lecithin cholesterol acyltransferase (LCAT) deficiency [100, 101]. Paroxonase 1 (PON1), a strong anti-atherogenic enzyme of HDL, activity has also been shown to be diminished in CKD [102]. PON1 concentration is significantly and positively associated with HDLc and Apo A1 [103]. PON1 activity was also shown to be lower in CAPD compared with hemodialysis [104]. PON1 activity in CKD subjects predicted a higher risk of incident long-term adverse CV events [105].

HDL Functional Changes

To demonstrate the functional changes of HDL in CKD, the biological activity of high-density lipoprotein particles in patients with chronic kidney disease (HDL-CKD) is compared with the same activity in healthy controls (HDL-H). HDL-CKD, but not HDL-H, promoted endothelial superoxide production, substantially reduced nitric oxide bioavailability in endothelial cells in vitro, and increased arterial blood pressure in mice [106]. HDL-H, but not HDL-CKD, inhibits the production of inflammatory cytokines by stimulated peripheral monocytes [107]. Compared with HDL-H, HDL-CKD increased the cytokine

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response and disrupted macrophage chemotaxis in human umbilical vein endothelial cells [108]. When the efflux capacity of HDL was tested directly, HDL-CKD from dialysis patients was dramatically less effective than normal HDL-H in accepting cholesterol from macrophages [109]. Statins had no effect on the impairment of HDL-mediated efflux. Cholesterol acceptor capacity of HDL-CKD from dialysis patients was confirmed to be markedly reduced compared with that of HDL-H [110].

Dyslipidemia in Patients with Renal Transplant

There is also a marked variability of lipoprotein concentrations in renal transplant patients [111]. This lipoprotein variability is at least in part attributable to medications used for graft survival, and also to the intensity of statin therapy.

Prednisone

Prednisone in transplanted patients treated with cyclosporin (CsA) resulted in increases in HDL cholesterol [112, 113]. High-dose prednisone resulted in decreased Lp(a) levels 1 week after transplantation [114]. As steroid doses were gradually tapered, Lp(a) concentrations subsequently increased. Transplanted patients treated with alternate day steroids had a significant decrease in both serum TG and TC [115].

Calcineurins

The drugs from this class are CsA and tacrolimus (TAC), and each have a very different metabolic profile. When transplanted patients are treated with prednisone, with or without CsA, the patients receiving CsA demonstrated increased plasma concentrations of LDLc [116]. CsA blood levels are inversely associated with serum Lp(a) levels in renal transplant recipients; this association is independent of prednisone therapy [117]. CsA therapy has opposing effects on plasma Lp(a) and LDLc accumulations. Replacing CsA with TAC, in one study of transplanted patients, resulted in significant decreases in TC, LDLc, and ApoB levels [118]. In other studies, a switch from CsA to TAC significantly decreased TG, ApoB, LDLc, and TC levels [119, 120]. Changes in HDLc in these studies were variable. In a small randomized trial of CsA versus TAC in renal transplantation, the CsA treatment group had significant increases in TC, TG, LDLc, and HDLc [121]. However, the advantages of TAC over CsA in terms of hyperlipidemia should be balanced against the risk of new onset diabetes [122, 123].

Mammalian Target of Rapamycin Inhibitors

The drugs from this class are sirolimus and everolimus, and they have a similar metabolic profile [124]. They are almost invariably used together with calcineurin inhibitors. Conversion of transplanted patients from TAC to sirolimus resulted in a significant increase in TC, LDLc, and TG [125, 126]. This effect is the result of reduced catabolism of Apo B100-containing lipoproteins [127]. During sirolimus uptitration, TG, Apo B100, and ApoC-III levels increased in a dose-dependent manner [128]. Sirolimus expands the free fatty acid pool, and therefore the incorporation of a labeled fatty acid, [13 C4]-palmitate, into TG of VLDL, IDL, and LDL was decreased. The authors suggested that sirolimus-related increased free fatty acid flow is due to an altered insulin signaling pathway resulting in an increased hypertriglyceridemia. Hyperlipidemia induced by sirolimus will also vary with the genetic polymorphism of adenosine triphosphate (ATP)-Binding Cassette (ABC)B1-3435, ABCB1-1236, and IL-10-1082 genes [129].

Lipid-altering Trials in CKD Patients

In 2011, the highly anticipated results of the largest study to date examining the effectiveness of statin therapy in patients with CKD were published. The Study of Heart and Renal Protection (SHARP) included 9270 CKD patients (4650 assigned to combined statin plus ezetimibe therapy and 4620 patients on placebo) [130] aged 40 years or older with no known history of MI or revascularization; 3056 of the patients were on dialysis at the time of study entry. Unlike other prior statin trials that only included NDD-CKD stage 3 patients or dialysis patients, SHARP notably expanded the criteria to include not only those two groups but additionally patients with NDD-CKD stage 4 (41% eGFR 15–29 ml/min/1.73m^2) and stage 5 (20% eGFR < 15 ml/min/1.73m^2). The study had enrollment sites worldwide and included 72% White, 3% Black, 23% Asian, and 3% other or unspecified patients. The mean ± SD age of enrolled patients was 62 ± 12 years, and 31% of patients were age 70 or older. The study's primary outcome of interest was first major atherosclerotic event (nonfatal MI or coronary death, non-hemorrhagic stroke, or any arterial revascularization procedure). Compared to patients on placebo, patients in the simvastatin plus ezetimibe treated arm had a 17% reduction in major atherosclerotic events,

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25% reduction in nonhemorrhagic stroke, and 21% reduction in arterial revascularization procedures. However, there was no difference in the number of coronary deaths, and differences in the number of nonfatal MIs did not reach statistical significance. Subgroup analysis revealed the outcome risk reductions were larger in patients with higher baseline BMI, TC, and LDLc. Strikingly, there was an incrementally lower benefit as CKD progressed with lower eGFR levels or higher excreted microalbumin; however, subgroup analysis did not show significant heterogeneity across these groups. In the SHARP study, there was no excess risk of adverse events for patients on statin therapy.

Soon after the results of the SHARP trial were published, meta-analysis studies pooled the results of statin trials in CKD patients (including SHARP) to determine statin efficacy. Palmer et al., as part of the Cochrane collaboration, reviewed over 50 studies with over 45 000 CKD patients and found that statin therapy in NDD-CKD reduced the risk of major CV events by 18%, risk of all-cause mortality by 21%, risk of CV mortality by 23%, and risk of MI by 45% [131]. The study was not able to find an association between statin therapy and stroke prevention. Although the meta-analysis was not able to thoroughly evaluate potential harms from statin therapy due to lack of systematic reporting of adverse events across studies, no significant association between statin therapy and adverse events, including elevated creatinine kinase, liver function abnormalities, and cancer, was found in the limited data that was available. Similarly, Hou et al. also conducted a meta-analysis that included 31 trials and nearly 50 000 patients with CKD and found that statin therapy reduced CV events by 23%, coronary events by 18%, and all-cause and CV deaths by 9%, but no significant associations were found for stroke or adverse events, including liver function or muscular disorders [132]. Moreover, Hou et al. corroborated the findings of the SHARP trial in demonstrating a decreasing benefit of statin therapy across worsening CKD stage. The meta-analysis found that for CKD stage 3 (which also included two small studies of CKD stage 2 patients), stage 4 (which included one other study aside from SHARP), and stage 5 NDD-CKD (SHARP only) CV outcomes were reduced by 31%, 22%, and 18%, respectively, for statin-treated patients compared to placebo patients.

Statins in Hemodialysis

The SHARP trial also included 3023 patients on dialysis, of which 84% were hemodialysis patients. The study showed there was no heterogeneity of effect for the efficacy of the treatment between dialysis and NDD-CKD patients. However, because the risk ratio for the dialysis subgroup did not reach statistical significance (RR 0.90, 95% CI 0.75, 1.08), many clinicians have interpreted this finding to show that the combined simvastatin plus ezetimibe therapy compared to placebo failed to reduce major outcomes in dialysis patients. Two other larger trials previously evaluated the benefit of initiating statin therapy in dialysis patients. The Deutsche Diabetes Dialyse Studie (4D) [133] enrolled 1255 type 2 diabetic patients on maintenance hemodialysis (median dialysis vintage 8 months) and randomized them to receive either 20 mg of atorvastatin daily or placebo. Lipid-lowering benefit was observed in the statin-treated group after only 4 weeks of the trial, where LDL was reduced by 42% in statin-treated patients. However, after a median follow-up of 4 years there was no difference in primary endpoints (composite of death from cardiac causes, nonfatal MI, and stroke). When outcomes were evaluated separately, statin patients had a reduced risk of all cardiac events, no difference in all-cause mortality risk, but a higher risk of fatal stroke. The Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events (AURORA) [134] also investigated the effects of statin (rosuvastatin 10 mg/day) versus placebo therapy; this study included 2776 hemodialysis patients (median dialysis vintage 3.5 years) aged 50–80 years. Similar to 4D, after 3 months the LDL in the statin-treated group had reduced by 43% compared to 2% in the placebo group. However, also similar to 4D, after a follow-up of 3.8 years there was no benefit of statin in reducing the primary endpoint (death from CV causes, nonfatal MI, or nonfatal stroke). Statins also had no effect on the individual components of the primary endpoint and no significant effect on all-cause mortality.

The Hou et al. meta-analysis also examined associations of statin therapy with outcomes in dialysis patients (including the above three trials) and determined that although there was a lack of a significant association for mortality outcomes in the dialysis patients, there was no heterogeneity of effect for all-cause mortality or CV death between dialysis and NDD-CKD patients. However, associations did differ for coronary event and stroke outcomes, which found no benefit of statin therapy for dialysis patients. There was also no heterogeneity of effect between dialysis and NDD-CKD for adverse event outcomes, including liver disorders, creatinine kinase elevation, new cancer onset, muscle pain, and serious adverse events [132].

Statins in Peritoneal Dialysis

Clinical trials examining statin initiation in peritoneal dialysis are limited. SHARP included only 496 peritoneal dialysis patients and failed to find a significant benefit of statin therapy

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in reducing the primary endpoint, although estimates trended toward statin benefit (RR 0.70, 95% CI 0.46, 1.08). However, a propensity score matched retrospective United States Renal Data System (USRDS) cohort study of 1053 peritoneal dialysis patients found that use of lipid-modifying medication (mostly statins) was associated with 26% and 33% lower risk of all-cause and CV mortality, respectively; this was particularly the case in patients with elevated cholesterol levels [135]. Additionally, a propensity score matched cohort analysis of 1024 Korean peritoneal dialysis patients found statin use was associated with 45% lower mortality risk [136]. As discussed above, peritoneal dialysis patients have higher levels of ApoB containing lipoproteins [137], and thereby statin benefit may be different in peritoneal patients compared to hemodialysis patients. Additional trials examining statin initiation in peritoneal dialysis patients and reduction of CV events should be undertaken.

The conclusion drawn from the dialysis trials as summarized by meta-analysis was that statin therapy appears to be ineffective in reducing CV events when initiated in patients already on dialysis. As will be discussed below, these trials provided the evidence to determine guidelines suggesting not to initiate statin therapy in dialysis patients, but to continue therapy after transition to dialysis when statins were already started in late-stage CKD. Although continuation of statin therapy has not been examined in a clinical trial, a recent cohort study [138] of US veteran patients transitioning to dialysis found that continuation of statin therapy after dialysis transition was associated with a 28% lower risk of all-cause mortality and an 18% lower risk of CV mortality in adjusted analysis compared to patients that discontinued statin use. As noted in the invited commentary for this study, this analysis is supportive of statin continuation, but not sufficient "until high-quality randomized clinical trials evaluating this question are conducted" [139].

Statins in Renal Transplant

The use of statins for prevention of CV events in renal transplant patients has to date only been tested in one clinical trial. The Assessment of LEscol in Renal Transplantation (ALERT) trial randomized 2102 renal transplant recipients to fluvastatin 80 mg/day versus placebo and compared the risk of the primary endpoint (cardiac death, nonfatal MI, or coronary revascularization) [140]. After a mean of 5.1 years, LDLc was lowered by 32% in statin-treated patients; however, risk reduction for the primary endpoint was not significant. There were, however, fewer cardiac deaths or nonfatal MI events in the fluvastatin group than in the placebo group. Coronary intervention procedures and other secondary endpoints did not differ significantly between groups. A post hoc analysis of ALERT found benefit of fluvastatin in reducing an alternative primary endpoint of cardiac death or definite nonfatal MI. In subgroup analysis for this endpoint, they also found significant benefit of fluvastatin in patients who were younger, nondiabetic, nonsmokers, and without pre-existing CVD. However, the authors caution that this subgroup analysis is exploratory and overlapping confidence intervals demonstrated no heterogeneity of effect across comparison strata [141]. Another post hoc analysis determined that 32% of patients enrolled in ALERT had MetS and risk of major adverse CV events were reduced by 53% in this group, thereby potentially identifying a group of renal transplant recipients who may benefit from statin therapy. When the study investigators conducted an additional post hoc analysis on patients who were less than 4.5 years after renal transplant at study baseline, they found risk of cardiac death and nonfatal MI was reduced by 56% and concluded the analysis supported introduction of statin therapy early in the post-transplant period [142]. Lastly, an extension study offered open label fluvastatin for two additional years to patients who completed the ALERT trial and included 1652 (92%) of ALERT trial participants. Patients randomized to fluvastatin had a 29% reduction in cardiac death or definite nonfatal MI [143]. A meta-analysis by Palmer et al. summarized statin trials in renal transplant recipients, including the ALERT study, and suggested that statin therapy may reduce CV endpoints, however the current data lacks precision to confirm any benefit and further trials are needed [144].

Statins and Progression of CKD

The benefit of statin therapy in reducing progression of CKD has been examined in most clinical trials; however, the results have been conflicting. In the meta-analysis by Palmer et al. no conclusions could be made about whether statin therapy slowed CKD progression. Although the analysis found a significant benefit of statin therapy on decreasing proteinuria, there was no benefit found for reducing the number of patients transitioning to ESRD. This latter analysis was based solely on the results of the SHARP trial. Another meta-analysis similarly found a benefit of statins in reducing proteinuria outcomes in patients with urinary protein excretion of 30 mg/day or more [145]. They also found that CKD patients receiving statin therapy compared to placebo had less of an eGFR reduction by study end; however, these results seem largely influenced by one study as no benefit was observed in the other nine studies included in the analysis. A more recent meta-analysis by Sanguankeo et al. supported these latter results, finding that statin therapy was associated with a modestly slower

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eGFR change per year as compared to placebo. They further found that these results were driven by significant findings for high-intensity statins as no significant difference in change in eGFR was found for low or moderate intensity statins. However, in this meta-analysis they found the data were insufficient to study impacts on proteinuria. Other studies have claimed differences in preserving renal function according to statin type or brand [146–148]. To date, the data on the effects of statin on progression of CKD and protein excretion are variable and modest. Additional data are needed to conclude whether statins provide renal protection in patients with CKD.

Statins and Adverse Outcome/ Safety in CKD

Statin safety may be of particular concern in CKD patients who typically also have higher comorbidity and polypharmacy, and may have a higher rate of metabolite accumulation due to decreased renal function and uremia-related muscle injury that could increase risk of myopathy [149]. As mentioned above, results of the meta-analyses evaluating the safety of statin therapy in CKD patients (both non-dialysis and dialysis) demonstrated no excess risk of adverse events such as elevated creatinine kinase, liver function problems, muscle disorders, or cancer onset with statin treatment. Palmer et al., however, noted lack of systematic reporting may contribute to the inability to thoroughly evaluate adverse events. A recent statement from the ACC further supported findings of no excess risks and summarized concerns of statin safety [150]. The report found risk of events including hepatotoxicity, rhabdomyolysis, and new onset of diabetes to be very low at 0.2% or less per year and found no convincing evidence of risk of cancer, cataracts, cognitive dysfunction, peripheral neuropathy, erectile dysfunction, or tendonitis with statin use. In CKD and in particular in both hemodialysis and peritoneal dialysis patients, statins appeared to be safe even in consideration of the polypharmacy in these patients. Although there was no excess risk reported for myopathy, one randomized clinical trial found CKD was a risk factor for myopathy in patients treated with simvastatin 80 mg. The statin safety report therefore provides a table summarizing how to modulate statin therapy with CKD progression and maximum dose per statin type in patients with mild to moderate CKD and ESRD to avoid myopathy risks. The report additionally addresses drug–drug interaction of cyclosporine and statin in renal transplant patients. Cyclosporine has been shown to increase blood levels of statins, which may increase risk of myopathy [151]. According to statin safety guidelines, cyclosporine should be avoided in patients treated with atorvastatin, simvastatin, lovastatin, and pitavastatin, and statin doses should be lowered in patients treated with cyclosporine and fluvastatin, pravastatin, and rosuvastatin.

Statin Dose

Caution for adverse events in CKD patients such as muscle disorders may lead clinicians to prescribe lower dose therapy. One post hoc analysis [152] in 2978 Japanese NDD-CKD patients without history of ischemic heart disease or stroke and moderate hypercholesterolemia evaluated the benefit of low-dose statin therapy (pravastatin 10–20 mg daily) versus placebo and found reduction in coronary heart disease events, all-cause mortality, and stroke. However, results of meta-analyses in CKD patients showed that benefit of statin is related to the strength of LDL lowering and therefore stronger therapy may still be indicated. Most clinical trial data included in the above-mentioned meta-analyses [132] of CKD patients included trials where patients received moderate dose statin therapy versus placebo. The SHARP trial used a combination of moderate dose statin plus ezetimibe, leading to more intense lipid-lowering therapy. To date, two post hoc analyses of randomized control trials have examined the benefit of more aggressive lipid lowering with high-dose statin in CKD patients. The Treating to New Targets (TNT) study [153] randomized patients to atorvastatin 80 mg/day (high dose statin) or 10 mg/day (moderate dose statin) and found the major CV endpoint was reduced by 32% for 3107 CKD (mostly stage 3) patients and reduced by 15% in patients with normal eGFR (median follow-up of 5 years). Moreover, the study reported no difference in safety concerns between the CKD and normal eGFR groups. In the Justification for the Use of statins in Prevention; an Intervention Trial Evaluating Rosuvastatin (JUPITER) primary prevention trial [154], high-dose statin (rosuvastatin 20 mg) was compared with placebo among men and women free of CVD who had LDLc <130 mg/dl and elevated high-sensitivity CRP. The post hoc analysis compared CV events in 3267 patients with moderate CKD at study entry and 14 528 with normal eGFR. After a median follow-up of 1.9 years, statin-treated CKD patients had a 45% reduction in the primary endpoint and a 44% reduction in all-cause mortality. Additionally, in CKD patients there were no differences between statin therapy and placebo for adverse events. However, statin-treated CKD patients had a statistically significant but not clinically different higher HbA1c at 24 months, but no differences in fasting glucose were observed. Although results in CKD patients were not specifically discussed, in another post hoc analysis of the JUPITER trial, Ridker et al. found that treatment with statin therapy was associated with a fast time to diagnosis of diabetes [155].

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Statins and Diabetes Risk

A number of meta-analyses have summarized statin trials in evaluating risk of incident diabetes and found statin treatment was significantly associated with an increased risk [156–160]. The magnitude of risk may differ depending on diabetes definition, statin dose [158, 159, 161] duration of exposure to statin therapy [162], and statin type [160, 163] and may further be explained by bias in competing risk of mortality in placebo treated patients [164]. The mechanism of action by which statins increase the risk of incident diabetes is not clear, and several mechanisms have been postulated [165–168]. To date, no study has directly examined risk of diabetes incidence in statin-treated patients with CKD. Authors of the cited studies [156–160] agree that risk of diabetes incidence does not outweigh the benefits of CV risk protection and improved survival with statin therapy. However, the overall safety of statins (in particular high-dose statin) in CKD patients still needs to be addressed in future studies.

Nonstatin Lipid Lowering in CKD

Although statin therapy is the main course of treatment for dyslipidemia, a number of studies have evaluated the potential benefits of nonstatin lipid-lowering therapies in CKD. The nonstatin lipid-lowering medications include those targeted at lowering cholesterol (bile acid binding resins, ezetimibe, PCSK9 inhibitors) and those altering lowering triglyceride and/or elevating HDL levels (fibrates, niacin, omega (n–3) fatty acids).

Cholesterol

Bile Acid Binding Resins

Bile acid binding resins, including cholestyramine, colestipol, and colesevelam, are another cholesterol-lowering medication often given to statin-intolerant patients. They are less potent than statins at decreasing TC and LDLc, and have been associated with an increase in TG level [169]. The Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT) randomized 3806 men free of coronary artery disease with elevated LDLc (>175 mg/dl) to cholestyramine with an intended dose of 24 g/day versus placebo [170]. After 7.1 years there was a significant 19% reduction in the incidence of nonfatal MI or coronary death. The average serum creatinine in enrolled patients was 1.03 mg/dl and effect modification by CKD was not conducted.

The phosphate binder, sevelamer, used in CKD patients to lower serum phosphorous levels was shown to act as a bile acid binder in CKD patients and lowered LDLc as well as increasing HDLc [171]. Colestilan, a phosphate binder used in Japan, was shown to be equivalent to sevelamer in phosphate binding and LDLc lowering efficacy [172] and similar to simvastatin in LDLc lowering [173]. The benefit of sevelamer in reducing adverse outcomes in CKD patients has been demonstrated [174–176]. One small study compared sevelamer versus calcium acetate in atorvastatin-treated dialysis patients and found greater LDL lowering in sevelamer-treated patients, but no difference in coronary artery calcium progression between treatment arms after 1 year [177]. Whether bile acid resins, including sevelamer, confer CV benefit in CKD patients already on statin therapy needs to be further evaluated.

Ezetimibe

Ezetimibe is another cholesterol-lowering medication that acts similarly to bile acid resins by decreasing cholesterol absorption. When added to statin therapy, ezetimibe can reduce cholesterol levels by an additional 23–24% on average. The Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) [178] evaluated the effect of ezetimibe combined with simvastatin, as compared with simvastatin alone, in 18 144 patients who had an acute coronary syndrome and whose LDL cholesterol values were within guideline recommendations. Over a median follow-up of 6 years, patients on the combined therapy had significantly greater benefit of LDL lowering and lower risk of the composite endpoint of nonfatal MI, unstable angina requiring rehospitalization, coronary revascularization (≥30 days after randomization), or nonfatal stroke. A post hoc analysis of IMPROVE-IT evaluated associations across eGFR levels and found patients with normal eGFR had a 12% risk reduction, while those with moderate CKD had a 13% risk reduction of the primary endpoint [179]. The analysis found no difference in change in mean eGFR over the 7 years of follow-up between study arms, yet also found no excess of adverse risk in the combined therapy patients. The results of this post hoc analysis combined with the SHARP trial results demonstrate the benefits of the combined statin plus ezetimibe therapy without any concerns of added risk in CKD.

PCSK9 Inhibitors

PCSK9 inhibitors have shown remarkable results in LDL lowering and CV benefits [180, 181].

The Long-term Safety and Tolerability of Alirocumab in High Cardiovascular Risk Patients with Hypercholesterolemia Not Adequately Controlled with Their Modifying Therapy (ODYSSEY LONG TERM) study randomized patients with high risk of CV events, LDLc ≥70 mg/dl, and receiving

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treatment with statins at the maximum tolerated dose to alirocumab versus placebo [181]. At week 24, the mean percentage change in LDLc from baseline for alirocumab versus placebo was 62%, and the treatment effect remained over the 78 weeks of follow-up. A post hoc analysis found that the rate of CV events (death from coronary heart disease, nonfatal MI, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization) was 48% lower in alirocumab-treated patients versus placebo. Patients with eGFR <60 ml/min/1.73m^2 for 3 months or more at the screening visit were included in the study as having a high risk of CV events; however, patients with eGFR <30 ml/min/1.73m^2 were excluded. A larger trial called ODYSSEY OUTCOMES randomized 18 924 patients aged 40 years or older to alirocumab versus placebo if they had acute coronary syndrome (acute MI or unstable angina) within 12 months prior to randomization, were on high-intensity statin, and had an LDLc ≥70 mg/dl. Patients with eGFR <30 ml/min/1.73m^2 were again excluded. At 4 months, alirocumab patients had a 56% greater LDLc reduction, which was maintained after the remaining course of follow-up. Over a median follow-up of 2.8 years, alirocumab-treated patients had a 15% lower risk of the primary endpoint (coronary heart disease death, nonfatal MI, ischemic stroke, or unstable angina requiring hospitalization). Patients also had a lower risk of all-cause death, but not CVD or coronary heart disease death. The results of this trial were presented at the 2018 American Cardiology Conference [182]. A post hoc analysis included eight of the earlier phase 3 ODYSSEY trials and found that among 4629 hypercholesterolemic patients (including 10% with impaired renal function), LDLc lowering and safety were comparable in CKD and non-CKD patients [183]. To date, information comparing clinical outcomes across CKD stages have not been presented for alirocumab.

The Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) trial then tested the impact of evolocumab when added to high-intensity or moderate-intensity statin therapy in 27 564 patients with clinically evident ASCVD and LDL ≥70 mg/dl [180]. At 48 weeks follow-up, the mean percentage reduction in LDLc with evolocumab, as compared with placebo, was 59% (95% CI: 0.58–0.60), with 87%, 67%, and 42% of patients in the evolocumab-treated group achieving LDLc <70, <40, and <25 mg/dl, respectively. After a median follow-up of 2.2 years, evolocumab versus placebo reduced the risk of the primary composite endpoint (CV death, MI, stroke, hospitalization for unstable angina, or coronary revascularization) by 15%. Patients with eGFR ≥20 ml/min/1.73m^2 were included in the study [184]. At the 2018 American Society of Nephrology Kidney Week Conference, Charytan et al. presented the results of a post hoc analysis comparing the efficacy and safety of evolocumab versus placebo across baseline CKD stages [185]. The analysis showed that the FOURIER trial was composed of 29%, 55%, and 16% of patients with eGFR ≥90, 60–89, and <60 ml/min/1.73m^2, respectively. LDLc reduction with evolocumab versus placebo at 48 weeks, relative risk of the primary endpoint, and adverse events including eGFR decline was similar across CKD groups. They also found that absolute relative risks for the secondary endpoint (composite of CV death, MI, or stroke) were larger among those with eGFR <60 ml/min/1.73m^2, as compared to patients with eGFR ≥90 ml/min/1.73m^2.

PCSK9 inhibitors may have a great future in treating dyslipidemia in patients with CKD, although concerns have been raised regarding the affordability of this drug. Further studies are needed, in particular in dialysis and renal transplant patients.

Triglyceride/HDL

Fibrates

CKD patients with elevated TG may need additional or other lipid-lowering therapy as statins have been shown to only modestly reduce TG. Fibrates (including gemfibrozil and fenofibrate) have been used in clinical practice to decrease TG levels, modestly improve HDL, and reduce CV events. The Helsinki Heart Study [186] and the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT) [187] demonstrated a reduction in CV events (fatal and nonfatal MI, and nonfatal MI or death from coronary causes, respectively) in fibrate-treated patients compared to placebo. However, in the larger Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial, which included 9795 patients, fenofibrate did not reduce the primary endpoint (coronary heart disease death or nonfatal MI) but did significantly reduce nonfatal MI by 24%, total CV disease events by 11%, and coronary revascularizations by 21% [188]. The authors of the trial speculated that higher rates of off-protocol initiation of statin therapy in placebo-allocated patients may have masked a moderately larger treatment benefit. A meta-analysis addressed data concerning patients with CKD enrolled in VA-HIT and FIELD as well as other studies (10 studies, 16 869 CKD patients) [189] and found fibrates improved lipid profiles and reduced major CV events and CV deaths but not all-cause mortality and stroke in patients with mild to moderate CKD. The analysis also reported fibrates reduced albuminuria and reversibly reduced serum creatinine; however, it found no clear effect of preventing progression to ESRD.

In clinical practice, fibrates are typically recommended in addition to statin therapy. The Action to Control CV Risk

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in Diabetes (ACCORD) study evaluated the added benefit of fenofibrate versus placebo to statin in 5518 type 2 diabetic patients being treated with open-label simvastatin and found no benefit for fibrates in reducing CV outcomes [190]. In a post hoc analysis, which included 1910 patients with mild to moderate CKD and 3554 with normal eGFR, fenofibrate conferred no benefit in patients with CKD for primary or secondary outcomes [191]. However, in the non-CKD patients alone, the fenofibrate patients had a 36% reduction of CV mortality and a 44% lower rate of fatal and nonfatal congestive heart failure. Some studies have cautioned that the combined therapy may lead to safety concerns, such as rhabdomyolysis [192], but pharmacokinetic studies failed to show any changes in statin kinetic parameters when fenofibrate was tested against each statin separately [193–195]. Current Kidney Disease: Improving Global Outcomes (KDIGO) guidelines suggest that combined statin and fibrate therapy should not be used in patients with renal impairment due to concerns of adverse events and statin should be prescribed if trying to choose between the two medication classes [196]. However, if indicated, Canadian guidelines suggest that fibrates alone may be used in patients with mild CKD at lower doses (one-third of the normal dose) [197]. Additional studies may be needed to further evaluate whether the potential benefit of fibrate added to statin therapy in CKD patients outweighs any potential risks.

Niacin

Similar to fibrates, niacin is used to increase HDLc and reduce TG concentration. Early trials demonstrated that niacin added to statin monotherapy resulted in a reduction of carotid intima thickness, a marker of atherosclerosis. However, clinical trials failed to show CV benefit and introduced concerns regarding niacin safety. The Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides and Impact on Global Health Outcomes (AIM-HIGH) study enrolled 3414 patients with coronary artery disease (men below 40 mg/dl and women below 50 mg/dl) and high TG (over 150 mg/dl) with LDLc lowered to 40–80 mg/dl with simvastatin and ezetimibe, and randomized them to additional niacin or placebo therapy [198]. The primary endpoint evaluated was the first event of the composite of death from coronary heart disease, nonfatal MI, ischemic stroke, hospitalization for an acute coronary syndrome, or symptom-driven coronary or cerebral revascularization. After 36 months of follow-up, despite lipid improvement, there was no clinical benefit in reducing the primary endpoint from the addition of niacin to statin therapy. However, a post hoc analysis identified a subgroup of 439 patients with elevated TG (>200 mg/dl) and lower HDL (<32 mg/dl) that had a significant decrease in primary events, suggesting more extreme thresholds for enrollment should be used for niacin therapy [199]. Another post hoc analysis evaluated the efficacy of niacin in patients with stage 3 CKD and found no benefit in CV outcomes and a higher all-cause mortality risk in niacin-treated patients [200].

The Treatment of HDL to Reduce the Incidence of Vascular Events (HPS-THRIVE) trial enrolled 25 673 statin-treated patients with ASCVD and randomized them to niacin/laropiprant versus placebo [201, 202]. The study failed to show any benefit of the niacin therapy in reducing major CV events. Moreover, patients in the niacin therapy group had a higher risk of adverse events, including disturbances in diabetes control, diabetes incidence, and adverse events related to gastrointestinal and musculo-skeletal systems, skin, infection, and bleeding. Of note, the study included patients with a wide range of lipid levels who may not be indicated for niacin therapy, including over 49% of trial patients with an HDL ≥43 mg/dl and 74% with TG levels of <151 mg/dl.

Although a small pharmacokinetic study demonstrated that niacin may not need dose adjustments in patients with CKD [203], current KDIGO guidelines have stipulated that nicotinic acid has not been well enough studied in CKD, and given the risks of toxicity, it is currently not recommended for treatment of high TG [196]. Two review articles have summarized the beneficial properties of niacin, including anti-inflammatory properties, reducing serum phosphorous levels, and preventing HDL dysfunctionality [204, 205]. This suggests potential benefit of niacin therapy in patients with CKD, although further studies are needed.

Omega (n-3) Fatty Acids

Omega-3 fatty acids have also been used to target lowering of TG levels. The active ingredients include eicosapentanoic acid (EPA) and docosahexaenoic acid (DHA). In addition to dietary recommendations to consume fish rich in omega-3 fatty acids, there are two prescription strength medications on the US market: Lovaza, containing 375 mg DHA and 465 mg EPA, and Vascepa, containing 1 g purified EPA. A study found that the EPA-only Vascepa decreased LDLc, while the DHA-containing Lovaza increased it [206].

Clinical trials of omega-3 fatty acids for CV endpoints have yielded mixed results. The Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico-Prevenzione (GISSI-Prevenzione) study enrolled 11 324 survivors of MI and randomized them to Lovaza 1 g/day versus placebo [207, 208]. After 3.5 years, there was a significant 15% reduction in the combined endpoint of death,

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nonfatal MI, and stroke. Similar results were observed in a study of over 6000 heart failure patients [209]. However, additional studies that examined the clinical benefit of omega 3-fatty acids as an add-on therapy to statins failed to show clinical benefit in patients with a history of MI [210–212]. The Japan EPA Lipid Intervention Study (JELIS) randomized 18 645 patients with or without pre-existing coronary artery disease and a serum cholesterol >250 mg/dl to statin plus either 1800 mg EPA or placebo [213]. After 4.6 years, there was a significant reduction in the risk of major coronary events and nonfatal coronary events (19% each), a 28% decrease in the risk of unstable angina, and a 20% reduction in stroke in treated patients [214, 215]. Renal patients were excluded from the study. A more recent trial randomized 8179 statin-treated patients with established CVD, diabetes, or other risk factors and a fasting TG of 135–499 mg/dl and LDLc of 41–100 mg/dl to Vascepa or placebo. The study found that EPA-treated patients had a 25% lower risk of the primary endpoint (CV death, nonfatal MI, nonfatal stroke, coronary revascularization, or unstable angina) [216]. Patients with CKD, except those requiring dialysis, were included in the trial and stratification by eGFR showed no heterogeneity of effect.

Hemodialysis patients have markedly lower levels of plasma EPA and DHA when compared with NDD-CKD patients [217]. DHA has been shown to be an independent predictor of all-cause mortality [218] and of sudden cardiac death [219] in hemodialysis patients. A small trial randomized 206 hemodialysis patients to low-dose omega-3 fatty acids versus placebo, and found a small but significant reduction in the number of MIs (four versus 13, $P = 0.036$) in the treated versus placebo arms [220]. The Fish Oil Inhibition of Stenosis in Hemodialysis Grafts (FISH) study enrolled 201 patients and randomized them to fish oil (four 1 g pills per day) versus placebo for 12 months. In the fish oil group, there were half as many thromboses, fewer corrective interventions, and improved CV event-free survival [221].

Although the benefits of omega-3 fatty acids are promising in CKD and dialysis patients, further studies in larger trials are needed.

Guidelines

Guidelines advising on dyslipidemia slightly differ whether approaching from a nephrology angle using KDIGO guidelines [196] or a cardiology angle using ACC/AHA guidelines (Table 34.1). According to the 2018 ACC/AHA guidelines, CKD with an eGFR <60 ml/min/1.73m^2 is considered a risk-enhancing factor, and thereby adults aged 40–75 years with LDLc 70–189 mg/dl who are at 10-year ASCVD risk of 7.5% or higher should be treated with a moderate intensity statin with possible combination with ezetimibe [3]. For patients transitioning to dialysis, continuation of statin therapy is recommended. However, because the trials failed to show benefit of statin initiation in dialysis patients, initiation of statin in dialysis is not recommended. This is an update from previous guidelines, which did not have a recommendation regarding initiating or continuing statins in hemodialysis patients [222]. Similar to the current ACC/AHA guidelines, KDIGO guidelines recommend initiation of statin treatment with a statin or statin/ezetimibe combination in adults aged ≥50 years with eGFR <60 ml/min/1.73m^2, but not treated with chronic dialysis or kidney transplantation. Statin initiation is also recommended in NDD-CKD non-transplanted adult patients aged 18–49 years if they have known coronary disease, diabetes mellitus, prior ischemic stroke of >10% estimated 10-year risk of coronary death, or nonfatal MI. Similar to the ACC/AHA guidelines, KDIGO guidelines also suggest statins not be initiated, but should be continued in dialysis-dependent CKD. They also suggest treatment with statin in adult kidney transplant recipients. Current ACC/AHA guidelines do not have suggestions for renal transplant recipients. For statin therapy dosing in CKD patients, where statins are recommended, KDIGO guidelines provide a table which has dosing recommendations per statin type that corresponds with ACC/AHA guidelines of moderate statin doses. The ACC/AHA guidelines indicate there is a need for randomized control trials testing the efficacy of higher dose versus moderate dose statins in patients with risk-enhancing factors, which includes CKD. A recent cohort study in US veterans demonstrated no difference in the association of statin dose with mortality outcomes across stages of NDD-CKD [223].

For TG lowering, the KDIGO guidelines advise therapeutic lifestyle changes, and caution against the use of statins in combination with fibrates in CKD patients due to increased risk of adverse events. The 2013 ACC/AHA guidelines state that gemfibrozil should not be used in combination with statin, and for TG lowering a fenofibrate can be prescribed with dose alterations according to CKD stage: not to exceed 54 mg/day in patients with eGFR 30–59 ml/min/1.73m^2 and to discontinue when eGFR is persistently <30 ml/min/1.73m^2. Although there is currently a lack of data to support any guideline recommendation, niacin and omega-3 fatty acids may be used in place of fibrates, with monitoring of potential adverse reactions; however, further studies in CKD patients are needed.

Conclusion

The lipoprotein profile in CKD patients is variable depending on CKD stage, other patient characteristics including nutritional status, and management of the patient including

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Table 34.1 Recommendations for treatment of dyslipidemia.

Treatment	Recommendation	Certainty of evidence	Strength of recommendation
Statins for NDD-CKD patients, age <80 years	All NDD-CKD patients aged 50–80 years should be treated with a high-dose statin or a moderate dose statin ± ezetimibe irrespective of serum cholesterol. Younger patients should be treated if they have documented ASCVD, diabetes, or estimated 10-year risk of coronary death or nonfatal MI >10%.	High for total mortality, CV mortality, and MACE	Strong. Level A Class I.
Statins for hemodialysis patients	Statins should not be initiated in hemodialysis patients. Statins should be continued in transition to hemodialysis for predialysis patients.	High for noninitiation; low for continuation of statins	Strong for noninitiation. Level A Class III, no benefit. Weak for continuation. Level B Class IIa.
Statins for peritoneal dialysis patients	Statins may be initiated in peritoneal dialysis patients when cholesterol is elevated (>225 mg/dl).	Weak and only for total mortality	Weak for total mortality. Level C Class IIb.
Statins for renal transplant patients	Statins should be initiated in renal transplant patients, although there are increased risks due to drug interactions.	Weak for initiation and only for MACE; high for drug interaction	Weak for initiation. Level C Class IIa.
Statins for patients age >80 years	Statin initiation or continuation could be considered if the patient or family agrees and the long-term benefit exceeds the risks. Informed consent discussion is necessary.	Weak for initiation or continuation	Weak evidence. Level C Class IIa.
Fibrates	Fibrates are considered not effective as an add-on to statins in CKD patients unless triglycerides are >500 mg/dl.	Weak for use with triglycerides >500 mg/dl	Weak evidence. Level C Class IIb.
Niacin	Niacin should not be used for treatment of dyslipidemia in CKD patients.	Moderate for mortality	Moderate evidence. Level C Class III no benefit/harm.
Omega-3 fatty acids	EPA should be used in NDD-CKD patients with stage 3 CKD in addition to statin therapy if triglycerides are >135 mg/dl	Moderate for total and CV mortality and MACE	Moderate evidence. Level B Class I.
Ezetimibe	Ezetimibe should be added to statin therapy in CKD patients if the LDL cholesterol was not decreased by 50% and/or if LDL cholesterol is not at goal.	High for CV mortality and MACE	Strong evidence. Level A Class I.
Bile acid binding resins	Bile acid binding resins should not be used for dyslipidemia in CKD patients.	Weak	Low evidence. Class C Level III possible harm.
PCSK9 inhibitors	PCSK9 inhibitors should be used in patients with stage 3 CKD and ASCVD who have a LDL cholesterol >70 mg/dl on maximum tolerated dose of statin + ezetimibe.	Strong for CV mortality and MACE	Strong evidence. Class A Level I.

ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CV, cardiovascular; EPA, eicosapentanoic acid; LDL, low-density lipoprotein; MACE, major adverse cardiovascular event; MI, myocardial infarction; NDD-CKD, nondialysis dependent chronic kidney disease; PCSK9, proprotein convertase subtilisin/kexin type 9.

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type of dialysis and drugs aimed at prevention of graft rejection. Consequently, the ability of the different lipoproteins to predict adverse outcomes is limited. Interpretation of the levels should be individualized. Moderate dose statins should be initiated in patients with NDD-CKD and continued after patients transition to dialysis. The clinical benefit of statin currently outweighs the risk of adverse events in CKD patients. Further study is needed to ascertain the efficacy and possible risk of higher dose statins or nonstatin lipid-altering medications in CKD patients.

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35

Chronic Kidney Disease and Hypertension

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Introduction

Hypertension (HTN) is not only highly prevalent in patients with chronic kidney disease (CKD), it is also one of the most prevalent causes of progressive kidney injury and end-stage kidney disease (ESKD). This makes HTN a central issue in the treatment of the patient with CKD. Although it is clear that the renin angiotensin system (RAS), the sympathetic nervous system (SNS), and extracellular fluid volume (ECFV) expansion play a pivotal role in the pathophysiology of HTN in CKD, HTN remains uncontrolled in many patients. Clinically, blood pressure (BP) measurements in CKD are more complex than in essential hypertension because of the frequently disturbed diurnal rhythms. Angiotensin converting enzyme inhibitors (ACEis) and angiotensin receptor blockers (ARBs) are mainstay therapies for HTN in CKD to prevent progression of kidney failure. Diuretics are underutilized but can substantially contribute to better BP control in CKD. It is not clear whether newer therapies like baroreceptor stimulation and kidney denervation have utility in CKD. We propose an approach to the treatment of HTN in CKD based on the pathophysiology of HTN in CKD. For information about management of HTN in transplant recipients, and patients on hemodialysis or peritoneal dialysis, refer to Chapters 22 and 42.

Epidemiology

In this chapter, HTN in CKD is defined as having a BP of >130/80 mmHg or being on antihypertensive treatment [1]. This threshold is based on the recent literature, as discussed below, with the revision of several guidelines as a consequence. With increasing severity of kidney disease, the prevalence of HTN becomes progressively higher such that most patients with end-stage renal disease (ESRD) will become hypertensive.

Besides uncontrolled HTN, it seems relevant to consider resistant HTN (rHTN) [2]. Several definitions are relevant here. The term "apparent treatment-resistant hypertension" is defined as BP not at goal when the patient is prescribed ≥3 classes of antihypertensive medication or at goal after prescription of ≥4 classes. Of note, the most recent position paper on rHTN by the American Heart Association does not mention an actual BP level, but defines rHTN as the BP of a hypertensive patient that remains elevated "above goal" [3]. It is quite likely that over the next few years the BP level for defining rHTN could be adjusted as a result of the new insights about HTN appearing in the literature (see below).

The prevalence of apparent treatment-rHTN amounts to 2–10% in the general population [4, 5]. Data from the Chronic Renal Insufficiency Cohort (CRIC) study indicate that the prevalence is substantially higher in patients with CKD [6]. In the study, 40% of participants had apparent treatment-rHTN, with half of them not at target BP on ≥3 medications and the other half at target BP on ≥4 medications. This leads to questioning how many patients have "true" rHTN. Judd and Calhoun defined true rHTN as "a properly measured office BP >140/90 mmHg with a mean 24-hour ambulatory BP >130/80 mmHg in a patient confirmed to be taking ≥3 antihypertensive medications" [7]. The difference with the definition of apparent resistant hypertension is that here, BP is "properly measured" and not derived from sources where the assessment of BP is ill

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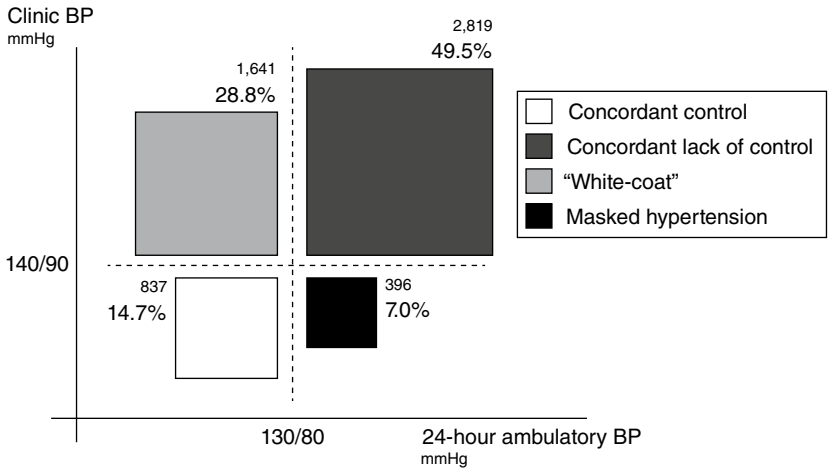

Figure 35.1 Prevalence of masked and white-coat hypertension in hypertensive patients with chronic kidney disease. *Source:* Reproduced with permission [13]. On the *x* axis, patients are divided into two groups: blood pressure (BP) <130/80 mmHg with 24-hour ambulatory BP or ≥130/80 mmHg. On the *y* axis, patients are also divided into two groups: clinic BP <140/90 mmHg and ≥140/90 mmHg. There are two groups where 24-hour ambulatory BP and clinic BP are discordant. One is the well-known white-coat hypertension: patients with normal BP at home (assessed with the 24-hour ambulatory BP assessment) and elevated in the clinic (assessed with the clinic BP). Less well recognized is masked hypertension: patients with normal BP in the clinic and elevated BP at home. *Source:* Gorostidi et al. [13]. © 2013, Elsevier.

defined, and that medication is "confirmed" and not "prescribed." While CKD is identified as a reason for true rHTN, it is currently not clear whether the prevalence of true rHTN is higher or lower than in people without CKD. It does not take away the relevance to investigate adherence if BP targets are not achieved with ≥3 antihypertensive medications.

A last issue is masked HTN, which is HTN that is present when the patient is at home, but is not measured as such in the office. The prevalence of masked HTN is estimated to be about 7–42% of hypertensive patients [8, 9] and is associated with an elevated cardiovascular risk [10]. By its nature, masked HTN can only be detected by ambulatory or home BP measurements. In a recent study with CKD patients, Agarwal defined masked HTN as having controlled HTN in the office (BP <140/90 mmHg), with elevated BP at home. Assessed by ambulatory BP measurements >135/80 mmHg during daytime, >130/80 mmHg during the entire day, or >120/70 mmHg during the night, overall prevalence of masked uncontrolled HTN was 56%. Assessed using average weeklong home BP measurements >135/85 mmHg, prevalence was similarly high at 51% [11]. A recent study from Europe reported a lower prevalence of 19% using ambulatory BP measurements [12]. These studies strongly emphasize the importance of home and ambulatory measurements. This is further illustrated in Figure 35.1.

Assessment of Blood Pressure

In the context of clinical evaluation of the patient with CKD, four different assessments of BP are being used: in-office manual, multiple in-office automated, home, and ambulatory measurements. Unfortunately, the level of BP is still often only derived from in-office manual measurements. These are notorious for inaccurate assessment of BP for a number of reasons, including white coat HTN (i.e. stress associated with a clinic visit), as well as the inability to diagnose masked or nighttime HTN. Multiple in-office automated measurements, if done appropriately with at least five measurements with the patient left alone seated in the right position in a quiet room, do resemble daytime ambulatory BP measurements. Although obviously more preferably than a single in-office measurement, it takes more time in the clinic, and masked or nighttime HTN still cannot be diagnosed. Since both masked and nighttime HTN are more prevalent in CKD patients [8, 9], this is obviously relevant. Home BP measurements have a number of benefits, including the possibility to have multiple measurements over the day and during work and weekend days. This facilitates the assessment of BP variability, including potential weaning of medication actions during some time of the day (e.g. becoming hypertensive before taking medications in the morning), and it enables the diagnosis of masked, but not nighttime hypertension. Furthermore, it engages patients in their care.

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Performing ambulatory BP measurements is more labor intensive, can be psychologically troubling for the patient, or even a bit painful, yet it provides day- and nighttime BP measurements, shows variations, allows coupling BP to symptoms, and avoids patient selection. Given the high prevalence of HTN in CKD, a strong call is being made to use ambulatory BP measurements more frequently in the assessment of BP in the CKD patient because of the issues with high prevalence of white coat, masked, nighttime, and variable hypertension. The pros and cons of different BP assessments are summarized in Table 35.1.

Table 35.1 Pros and cons of different approaches to assess blood pressure.

Issue	Office BP	Automated office BP	Home BP	ABPM
Affected by white-coat phenomenon	Yes	Possible	No	No
Able to detect white-coat hypertension	No	No	Yes[a]	Yes[a]
Able to detect masked hypertension	No	No	Yes[a]	Yes[a]
Easily available	Yes	Possible	Yes	Possible
Low cost	Yes	No	Yes	No

[a] When office measurements are also available.
BP, blood pressure; ABPM, ambulatory blood pressure measurements.

Pathophysiology

Three key mechanisms form an important basis for HTN in CKD: activation of the RAS and the SNS, and ECFV expansion. In addition, there are dozens of other BP modulating systems involved in the pathophysiology of HTN in CKD. Studies from the 1970s demonstrated elegantly that when renin levels are related to volume status, the baroreceptor curve is shifted upward: at any level of ECFV, renin is higher in CKD patients compared to controls. This activated RAS is more prominent in polycystic kidney disease [14], kidney involvement in scleroderma [15], as well as renovascular disease. The mechanisms by which angiotensin II leads to HTN are not only the classically described vasoconstriction and increase in aldosterone release but also encompass direct increases in proximal tubular reabsorption [16] and a number of indirect effects like increased oxidative stress with all its consequences and activation of the SNS. It has been nicely demonstrated that in CKD patients, ACE inhibition partly corrects the left shift of the baroreceptor curve.

Volume overload is the consequence of a too excessive sodium intake and the impaired ability of the kidney to excrete sodium at normal arterial pressures. Sodium intake to a certain extent is modifiable, yet in advanced kidney disease normotension cannot be maintained even at very low levels of sodium intake [17]. Effectively the pressure natriuresis curve has shifted to the right. At a tubular level, the activated RAS will enhance sodium reabsorption and the nephron is meanwhile unable to suppress its fractional reabsorption sufficiently. If glomerular filtration rate (GFR) decreases to 10% of normal, fractional sodium excretion would need to increase from about 1% to 10% to achieve sodium balance. It has become clear that volume overload is prevalent in CKD and hemodialysis patients now that reliable bio-impedance assessments are widely available [18, 19].

SNS activity is increased in CKD and ESRD. Initial observations by Converse demonstrated that nephrectomy diminished the activation of the SNS, as assessed by muscle sympathetic nerve activity [20]. Since then, sympathetic hyperactivity has been shown in nonproteinuric CKD as well as polycystic kidney disease. The hyperreactivity depends at least in part on the RAS, since in CKD patients ACE inhibition leads to normalization of sympathetic activity [21]. Surgical renal denervation has been shown to reduced BP in experimental CKD as well as in humans [22]. Denervation using an intravascular device has been less successful; however, technique improvements could resolve this [23]. Of note, sympathetic activation not only affects BP control but is also involved in a large number of processes, including glucose metabolism and insulin resistance, endothelial dysfunction and vascular stiffness, and immune modulation [24].

Besides this classical triad of mechanisms for HTN, CKD, and ESRD come with several other disturbances affecting BP regulation. Structural changes to the vasculature, including the classical Monkenberg media sclerosis, lead to increased vascular stiffness and peripheral resistance. This will affect both the BP and the pulse wave propagation and reflection, leading to increased cardiac afterload. Accumulation of the endogenous inhibitor of nitric oxide synthase (i.e. asymmetric dimethyl arginine [ADMA]), due to diminished breakdown, has been identified as a functional issue leading to high BP [25]. Functional abnormalities are also suspected in many BP-regulating systems, including the sensitivity to and handling of, among other factors, natriuretic peptides, eiconasoids, and endothelin. None of these potential mechanisms have currently been translated into therapy backed up by solid clinical investigation.

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Differential Diagnosis

A conundrum in the evaluation of the patient with HTN and CKD is that once CKD has developed, renal parenchymal HTN can obscure other forms of secondary HTN. This is difficult to decipher; however, it remains important if one wants to treat the HTN effectively and decrease the progression of kidney failure. For example, if a primary hyperaldosteronism has led to long-standing HTN and target organ damage including CKD, it is important that this is diagnosed and treated accordingly. However, diagnostic algorithms for primary hyperaldosteronism in moderate to advanced CKD do not have a solid evidence base, so one falls back on clinical evaluation and judgment: (relative) hypokalemia, alkalosis, and treatment resistance. If strongly elevated, a Plasma Renin activity (PRA) level might be helpful. Visualization of the adrenal glands and adrenal vein sampling will require an open discussion between care provider and patient.

Renal artery stenosis also leads to diagnostic and therapeutic dilemmas. Following the negative results of the STAR, ASTRAL, and CORAL trials about angioplasty and stent placement regarding treatment BP regulation and renal function [26–28], there is a strong reluctance to assess whether renal artery stenosis is present. If there is a suspicion of renal artery stenosis, there are at least three reasons to do additional investigations toward confirmation, despite these trials. First, fibromuscular dysplasia can present with impaired renal function and HTN, and is potentially resolvable [29]. Second, the three trials did not address whether patients with a rapid deterioration of renal function or with flash pulmonary edema could benefit from angioplasty and stent placement. Third, performing additional investigations could be performed if the kidney failure is unexplained. Although not very common, renal artery stenosis can present with a nephrotic range proteinuria. If kidney function is stable and BP is controllable, however, the three trials provide strong evidence not to do additional diagnostic testing or an intervention.

Table 35.2 lists a number of diagnoses that should be considered before HTN in a patient with CKD is labeled as renal parenchymal HTN.

Goals of Treatment of Hypertension in the Patient with CKD

Prevention of progression of CKD by HTN is one goal in the treatment of the HTN. There has been overwhelming evidence accumulated over the last 25 years supporting that fact that BP control reduces the progression of CKD.

A strong body of evidence supports the use of antihypertensive therapy, specifically with ACEi or ARBs, in patients with diabetic nephropathy (Table 35.3**)**. In 1993, the first large randomized control trial (RCT) to support this compared captopril versus placebo in preventing doubling of creatinine or reaching ESRD as primary outcome in patients with diabetic nephropathy [30]. The study demonstrated a decrease of 48% in reaching the outcome over the 3 years of follow-up. This study was followed by the Irbesartan in Diabetic Nephropathy Trial (IDNT) studying patients with type 2 diabetes, which demonstrated a better protection by Irbesartan for kidney disease progression than placebo or amlodipine [34] for a composite endpoint of doubling of creatinine or all-cause mortality. Similar findings were reported in the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) trial; here, a 16% reduction in risk to reach a composite renal outcome (doubling of creatinine or reaching ESKD) and death was observed in patients with diabetic nephropathy treated with losartan versus placebo [35]. A post hoc analysis of the RENAAL trial for renal outcomes separately indicated a benefit for patients with a high pulse pressure but was not straightforward in its interpretation [38].

Regarding nondiabetic nephropathy, there is also evidence that BP lowering slows progression of kidney disease. The aim of the African American Study of Kidney Disease and Hypertension (AASK) trial was to compare intensive versus less intensive BP lowering in African Americans with hypertensive kidney injury [36]. While the trial could not conclude that more intensive BP lowering had additional benefit to prevent the major outcomes (rate change of eGFR and progression of CKD or all-cause mortality), this trial concluded that there was specific benefit of an ACEi above a beta-blocker or calcium channel

Table 35.2 Secondary causes of hypertension to be considered in the patient with CKD.

System	Cause
Vascular	Atherosclerotic renal artery stenosis
	Fibromuscular dysplasia
	Aortic coarctation
Endocrine	Primary hyperaldosteronism
	Secondary hyperaldosteronism
	Cushing's syndrome
	Congenital adrenal hyperplasia
Tubular transport	Liddle's syndrome
	Gordon's syndrome
Other	Obstructive sleep apnea
	Severe obesity

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Table 35.3 Major trials on hypertension treatment in patients with CKD.

Study	Number of randomized patients	Primary aim	Study population	Study design	Outcomes evaluated	Duration of follow-up	Results	References
The effect of angiotensin-converting enzyme inhibition on diabetic nephropathy	409	To determine whether captopril has kidney-protecting properties independent of its effect on BP in diabetic nephropathy	Age: 18–49; IDDM for at least 7 years; serum creatinine ≤2.5 mg/dl; urine protein excretion ≥500 mg/24 h	DBRCT in 30 centers; captopril 25 mg PO TID ($n = 207$), placebo ($n = 202$); goal SBP <140 mmHg, DBP <90 mmHg	Primary: doubling of baseline serum creatinine to at least 2.0 mg/dl Secondary: length of time to the combined endpoints of death, dialysis, and transplantation and changes in kidney function	Median: 3 yr	Risk reduction for the primary endpoint was 48% in the captopril group Risk reduction was 50% for the combined endpoint in the captopril group	[30]
The effects of dietary protein restriction and BP control on the progression of CKD (MDRD)	Study 1:585; Study 2:255	To test whether restricting protein and controlling HTN delay the progression of kidney disease	Age: 18–70; serum creatinine (M) 1.4–7.0, (F) 1.2–7.0 mg/dl; MAP ≤125 mmHg; Study 1–GFR 25–55 ml/min, Study 2–GFR 13–24 ml/min Insulin-requiring diabetics and those with proteinuria >10 g/day were excluded	RCT in 15 centers Groups: usual (≤107 mmHg) or low MAP (≤92 mmHg); usual or low-protein diet (Study 1) and low and very low protein diet (Study 2) groups	Primary outcome: decline in GFR measured by I-iothalamate clearance, stratified by BP and proteinuria	Mean: 2.2 years	No difference in decline in GFR in both studies Among patients with higher baseline proteinuria, the low-BP group had a significantly slower rate of GFR decline in both studies	[31]
Effect of ramipril on decline in GFR and risk of terminal kidney failure in proteinuric, nondiabetic nephropathy (REIN)	352	To test the hypothesis that glomerular protein traffic, and its modification by an ACEi, influences kidney disease progression	Age: 18–70; Cr Cl 20–70 ml/min with variation <30% in previous 3 months; urine protein excretion >1 g/24 h for at least 3 months; no ACEi for at least 2 months before study	DBRCT Stratum 1: urine protein 1–2.9 g/24 h ($n = 186$) Stratum 2: urine protein ≥3 g/24 h ($n = 166$) Randomized to ramipril (1.25 mg) or placebo Dose increased every 2 weeks for a goal DBP <90 mmHg Other agents used as needed to achieve goal BP	Primary outcome: rate of GFR decline measured by iohexol clearance Secondary outcomes: urinary protein excretion and serum creatinine concentration Intention-to-treat analyses	Stratum 1: Median: 31 mo Stratum 2: Mean: 16 mo	Stratum 1: GFR decline per month not significantly different; significant reduction in proteinuria and progression to ESRD in the ramipril group Stratum 2: Decrease in the GFR decline per month was significantly lower in the ramipril than the placebo group (0.53 vs. 0.88 ml/min, $P = 0.03$) Significant reduction in proteinuria in the ramipril group that correlated inversely with GFR decline	[32, 33]

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Table 35.3 (Continued)

Study	Number of randomized patients	Primary aim	Study population	Study design	Outcomes evaluated	Duration of follow-up	Results	References
Renoprotective effect of irbesartan in patients with nephropathy due to type 2 diabetes (IDNT)	1715	To determine whether the use of an ARB or a CCB would provide protection against the progression of nephropathy due to type 2 diabetes beyond that attributable to the lowering of BP	Age: 30–70; type 2 diabetes; HTN–BP >135/85 or use of antihypertensive agents; urinary protein excretion of at least 900 mg/24 h; serum creatinine: (M) 1.2–3.0 mg/dl, (F) 1–3 mg/dl	DBRCT in 210 clinical centers; randomized to irbesartan ($n = 579$, dose titration 75–300 mg/day); amlodipine ($n = 567$, dose titration 2.5–10 mg/day); or placebo ($n = 569$)	Primary endpoint: composite of a doubling of the baseline serum creatinine, onset of ESRD, or death Secondary outcome: combined cardiovascular endpoint	Mean: 2.6 years	Risk of the primary composite endpoint in the irbesartan group was 20% and 23% lower than the placebo ($P = 0.02$) and amlodipine ($P = 0.006$) groups respectively No significant differences in death rates from any cause or the CV composite endpoint	[34]
Effects of BP level on progression of diabetic nephropathy (RENAAL)	1513	To assess the role of the angiotensin-II-receptor antagonist losartan in patients with type 2 diabetes and nephropathy	Age: 31–70, type 2 diabetes and nephropathy (urine albumin/creatinine ratio of ≥300 mg/g or proteinuria of ≥0.5 g/day); serum creatinine 1.3–3.0 mg/dl	DBRCT, multinational study, randomized to losartan (50–100 mg daily) or placebo, stratified by baseline proteinuria (urine albumin-to-creatinine ratio <2000 mg/g or ≥2000 mg/g) Additional open-label agents used as needed for goal BP <140/90 mmHg	Primary composite endpoint: time to doubling of serum creatinine, ESRD, or death, whichever occurred first Secondary endpoints: composite of morbidity and mortality from cardiovascular causes, proteinuria, and the rate of progression of kidney disease	Mean: 3.4 years	The losartan group had a 16% risk reduction in the primary endpoint (P=0.02 vs. placebo). Similar rates of death and cardiovascular morbidity and mortality in the two groups Losartan had a 35% reduction in proteinuria ($P < 0.001$, compared to placebo)	[35]
Effect of BP lowering and antihypertensive drug class on progression of hypertensive kidney disease (AASK)	1094	To compare effects of two levels of BP control and three antihypertensive drug classes on GFR decline in African Americans with HTN	Age: 17–80; African Americans; HTN; GFR 20–65 ml/min; nondiabetics	3 × 2 factorial design; randomized to usual (102–107 mmHg) or lower (<92 mmHg) MAP goal Treatment with metoprolol, 50–200 mg/day; ramipril, 2.5–10 mg/day; or amlodipine, 5–10 mg/day assigned in 2 : 2 : 1 ratio Additional open-labeled agents added sequentially	Primary endpoint: rate of change in GFR (GFR slope–acute and chronic) Secondary clinical composite outcome: GFR reduction by 50% or by 25 ml/min from baseline, ESRD, or death Other secondary outcomes: urine protein excretion, all CVE	3–6.4 years	There was no significant difference in mean GFR slope from baseline through 4 years in the two BP groups and the drug group comparisons The secondary clinical composite outcome was similar in the two BP groups, but the ramipril group had a 22% reduction compared to the other drug groups	[36, 37]

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Effects of BP level on progression of diabetic nephropathy (post hoc analyses of RENAAL)	1513	To evaluate the impact of baseline and treated SBP, DBP, and PP to assess the specific effect of losartan and the implications of dihyropyridine calcium channel blockers as concurrent therapy on composite and individual outcomes in patients with type 2 diabetes and nephropathy	Age: 31–70; type 2 diabetes and nephropathy (urine albumin/creatinine ratio of ≥300 mg/g or proteinuria of ≥0.5 g/day); serum creatinine 1.3–3.0 mg/dayl	DBRCT, multinational study, randomized to losartan (50–100 mg daily) or placebo, stratified by baseline proteinuria (urine albumin-to-creatinine ratio <2000 mg/g or ≥2000 mg/g) Additional open-label agents used as needed for goal BP <140/90 mmHg	Primary composite endpoint: time to doubling of serum creatinine, ESRD, or death, whichever occurred first	Mean: 3.4 years	Baseline SBP of 140-159 mmHg, compared to SBP <130 mmHg, increased risk for ESRD or death by 38% ($P = 0.05$) Patients randomized to the losartan group with a baseline PP >90 mmHg had a 35.5% risk reduction for ESRD or death ($P = 0.02$) compared to the placebo group	[38]
BP control for renoprotection in patients with nondiabetic chronic kidney disease (REIN -2)	338	To assess the effect of intensified vs. conventional BP control on progression to ESRD in patients with nondiabetic proteinuric nephropathies	Age: 18–70; nondiabetic nephropathy with persistent proteinuria (>1 g/24 h for at least 3 months); proteinuria of 1-3 g if Cr Cl <45 ml/min, and proteinuria ≥3 g if Cr Cl <70 ml/min	Multicenter RCT All received background ACEi therapy with ramipril Randomized to conventional (DBP <90 mmHg) or intensified (BP <130/80 mmHg) BP control Add-on therapy with felodipine in the intensified BP group	Primary outcome: time to ESRD over 36 months follow-up Secondary outcome: to compare the effects of two different levels of BP control on GFR decline, residual proteinuria, and fatal and nonfatal CVE	Median: 19 months	No significant difference in the progression to ESRD in the two BP groups ($P = 0.99$) No difference in the secondary outcomes between the two groups	[39]
Kidney outcomes in high-risk hypertensive patients treated with an ACEi or a CCB vs. a diuretic (ALLHAT post hoc analyses)	33 357	To determine whether, in high-risk hypertensive patients with a reduced GFR, treatment with a CCB or an ACEi lowers the incidence of kidney disease outcomes compared with treatment with a diuretic	Age: ≥55; stage 1 or 2 HTN with at least one other CAD risk factor; serum creatinine <2 mg/dl	DBRCT, post hoc analyses, randomized to receive chlorthalidone (12.5–25 mg/day), amlodipine (2.5–10 mg/day), or lisinopril (10–40 mg/day) in a 1.7 : 1 : 1 ratio Goal BP <140/90 in each arm by adding open-label agents as needed Stratified by baseline eGFR	Clinical kidney outcomes: development of ESRD or death from kidney disease Composite endpoint of ESRD or ≥50% decline in GFR from baseline; mean GFR during study follow-up	Mean: 4.9 years	No significant difference in the outcomes in patients taking chlorthalidone compared to those who received lisinopril or amlodipine, irrespective of the baseline GFR	[40]

(*Continued*)

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Table 35.3 (Continued)

Study	Number of randomized patients	Primary aim	Study population	Study design	Outcomes evaluated	Duration of follow-up	Results	References
Effect of a lower target BP on the progression of kidney disease: long-term follow-up of the MDRD study (post hoc analyses)	840	To assess the effects of a low target BP on kidney failure and all-cause mortality	Age: 18–70; serum creatinine (M) 1.4–7.0, (F) 1.2–7.0 mg/dl; MAP ≤125 mmHg; Study A: GFR 25–55 ml/min, Study B: GFR 13–24 ml/min	Long term follow-up of patients from 1993 to 2000 after the MDRD study ended (see above for MDRD study design)	Outcomes: kidney failure and a composite outcome of kidney failure or all-cause mortality, through extended follow-up	Approx. 7 years (1993–2000)	The adjusted hazard ratios in the low compared with the usual target BP group were 0.68 and 0.77 for development of kidney failure and the composite outcome, respectively	[41]
In the Action to Control Cardiovascular Risk in Diabetes blood pressure trial (ACCORD-BP); kidney subgrou p analysis	4678	Intense vs. standard therapy in patients with type 2 diabetes	Type 2 diabetes mellitus; hemoglobin A1C ≥7.5% Age ≥ 40 years with CVD; age ≥ 55 years with any of the following: atherosclerosis, albuminuria, LVH, ≥2 CV risk factors (dyslipidemia, HTN, smoking, or obesity) Exclusion criteria: BMI >45 kg/m^2; creatinine >1.5 mg/dl (132.6 umol/l)	Selection of the 2 × 2 design of the ACCORD study: standard (SBP <140 mmHg) vs. intense BP (SBP <120 mmHg) control; standard intense diabetes control	Primary outcome: composite endpoint, including both nonfatal and fatal CVD events (first occurrence of nonfatal myocardial infarction, nonfatal stroke, and cardiovascular death)	Mean follow-up: 4.7 years	No clear cardiovascular benefit of intense vs. standard therapy could be demonstrated, although the risk of stroke was reduced by 38% (HR 0.623, 95% CI 0.361-1.074)	[42]
Systolic Blood Pressure Intervention Trial (SPRINT)	9361	Intensive treatment (SBP <120 mmHg) vs. standard (SBP <140 mmHg) treatment	Age: >50 years; SBP ≥130 mmHg and increased cardiovascular risk, but without diabetes	Open-label RCT in 201 sites	Primary outcome: composite outcome of myocardial infarction, acute coronary syndrome not resulting in myocardial infarction, stroke, acute decompensated heart failure, or death from cardiovascular causes Kidney outcome in participants with CKD at baseline: composite of a decrease in the eGFR of 50% or more (confirmed by a subsequent laboratory test) or the development of ESRD	Median follow-up: 3.26 years	SBP of less than 120 mmHg, as compared with less than 140 mmHg, resulted in lower rates of fatal and nonfatal major cardiovascular events and death from any cause, although significantly higher rates of some adverse events were observed in the intensive-treatment group No difference in kidney outcome in intense BP treatment vs. standard group	[43]

ACEi: angiotensin-converting enzyme inhibitor; BMI: body mass index; BP: blood pressure; CCB: calcium channel blocker; CKD; CrCl: creatinine clearance; (also cr cl); CV: cardiovascular; CVD: cardiovascular disease; CVE: cardiovascular event; DBP: diastolic blood pressure; DBRTC: double-blind randomized controlled trial; ESRD: end-stage renal disease; GFR: glomerular filtration rate; (also eGFR: estimated glomerular filtration rate;); HTN: hypertension; IDDM: insulin dependent diabetes mellitus; M/F: male/female; MAP: mean arterial pressure; PP: pulse pressure; RCT: randomized controlled trial; SBP: systolic blood pressure.
Source: Modified from chapter on this subject in the previous edition (authors: Satyan and Agarwal).

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blocker in this setting. The smaller Ramipril Efficacy In Nephropathy (REIN) study addressed a similar question in proteinuric, nondiabetic nephropathy [32]. It studied whether BP lowering with an ACEi or with other therapy had comparable effect on proteinuria, slowing down kidney disease progression and preventing ESRD at the same level of BP control. Again, ACEi more so than other therapy decreased progression and prevented ESRD in the group with the lower level of proteinuria (the group with the higher level of proteinuria was discontinued because of strong benefit of ACEi during an interim analysis). In the patients receiving the ACEi, the percentage reduction in proteinuria was inversely correlated with decline in GFR. This review of trials is not exhaustive and more trials can be found in the literature, all stressing the importance of BP control to prevent CKD progression.

The other very important goal of treatment of HTN is the prevention of cardiovascular disease. In the Atherosclerosis Risk in Communities (ARIC) study cohort, progressive cardiovascular risk was reported in patients with mild to severe kidney disease that was independent from a large number of other cardiovascular risk factors [44]. That this is competing with the risk to reach ESRD was demonstrated in an epidemiological study showing that 1% of >11 000 patients with CKD stage 3 reached kidney replacement therapy, meanwhile 24% of the cohort passed away from cardiovascular disease; for CKD stage 4 these numbers were 18 and 46%, respectively [45]. This very clearly underscores the need to take both renal and cardiovascular protection into consideration for treatment. As mentioned, the IDNT and RENAAL trials support treatment of HTN for a composite renal and all-cause mortality outcome, the latter mainly being cardiovascular mortality.

The Action to Control Cardiovascular Risk in Diabetes-Blood Pressure (ACCORD-BP) trial investigated the effect of intense versus standard therapy in patients with type 2 diabetes, but it excluded patients with a serum creatinine level of more than 1.5 mg per deciliter (132.6 μmol/l). In the trial patients with mild to moderate CKD (stages 1–3B, $n = 4678$) no clear cardiovascular benefit of intense versus standard therapy could be demonstrated, although the risk of stroke was reduced by 38% (HR 0.623; 95% CI 0.361–1.074). The authors concluded that, given that the trial was not designed and powered to this purpose, an effect of intense BP control in patients with CKD could not be excluded [42].

In the Systolic Blood Pressure Intervention Trial (SPRINT), more than 9000 patients were randomized to intensive versus less intensive BP treatment where average systolic BP of 121 and 136 mmHg, respectively, were achieved [43]. When the trial was stopped early, more intensive treatment was associated with a significantly lower incidence of the composite outcome (defined as myocardial infarction, other acute coronary syndromes, stroke, heart failure, or death from cardiovascular causes). The hazard ratio with intensive treatment was 0.75 (95% CI 0.64–0.89). A post hoc analysis revealed that in about 2000 patients with CKD stages 3–4 the decrease in cardiovascular outcome was similar, with a hazard ratio of 0.72 (95% CI 0.63–1.05), and the hazard ratio for all-cause mortality was 0.72 (95% CI 0.53–0.99) [46]. This was not accompanied by more adverse events. Regarding the renal outcome, the composite of ≥50% decrease in eGFR from baseline or ESRD was not different between the intensive and less intensive groups (HR 0.90; 95% CI 0.44–1.83). As expected because of the larger drop in BP, the intensive group had a slightly higher rate of change in eGFR at 6 months into the study (−0.47 vs. −0.32 ml/min per 1.73 m^2 per year, $P < 0.03$). So, in this hallmark trial, more intensive treatment of patients with cardiovascular risk and CKD for more intensive BP lowering led to lower cardiovascular events, was not associated with higher adverse events, and was similar in kidney outcome. In light of the above, for cardiovascular more than kidney treatment goals, a lower BP target in CKD patients seems preferable.

Lifestyle Changes and Blood Pressure Control in CKD

Dietary Sodium

Despite the fact that ECFV expansion due to high sodium intake and impaired sodium handling by the kidneys in CKD are considered key factors in the pathogenesis of HTN in CKD patients, information on the role of sodium intake both in the progression of kidney disease and on cardiovascular event rate in CKD patients is limited. Regarding progression of kidney disease, Lambers Heerspink et al. demonstrated in an analysis of data pooled from the RENAAL and IDNT trials that a low sodium intake potentiated on the effect of angiotensin blocker not only to slow CKD progression but also to decrease cardiovascular events [47]. Further to cardiovascular outcomes, Mills et al. demonstrated that the higher urinary sodium excretion from multiple 24-hour urine collections in the CRIC study was associated with increased risk of cardiovascular events (composite of congestive heart failure, stroke, and myocardial infarction) [48]. There are no large-scale RCTs on the influence of dietary sodium restriction specifically aimed at CKD patients. It is necessary to mention the Dietary Approaches to Stop Hypertension (DASH) study since it provides solid evidence on the effect of dietary sodium restriction to lower BP; however, this study was not targeted to assess progression of CKD [49]. In 2015, a Cochrane review was published summarizing the effects of dietary sodium restriction on renal sodium excretion (to

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Table 35.4 Lifestyle management in the treatment of hypertension in chronic kidney disease (KDIGO Clinical Practice Guidelines).

Management	Recommendation	Certainty of evidence	Strength of recommendation
Lifestyle modification Sodium/salt	Lower or maintain salt intake to <90 mmol/day (equivalent to <2 g sodium/day or < 5 g sodium chloride/day)	C, low	1
Weight loss	Achieve or maintain a healthy weight (BMI 20–25)	D, very low	1
Exercise	Aim to exercise for at least 30 minutes five times per week	D, very low	1

evaluate whether the intervention was successful) and on kidney function [50]. Included in the analysis were eight studies, mostly nonrandomized, with the number of subjects ranging from 14 to 52 per arm. The three short-term (<4 weeks) and four out of the five long-term (≥4 weeks) studies indeed showed a significant decrease in urinary sodium excretion. Regarding kidney function, low dietary sodium did not decrease eGFR ($n = 2$ studies), creatinine clearance ($n = 3$), renal plasma flow ($n = 1$), or filtration fraction ($n = 1$); obviously the number of studies is very limited. BP and protein excretion were reduced by dietary sodium restriction. Only one study measured a decrease (0.8 l) in ECFV by reduction of sodium intake [51]; unfortunately, no changes in creatinine or eGFR were reported, so changes in volume status could not be related to changes in renal function. Although the data is lacking to strongly support that dietary sodium restriction in patients with CKD leads to a decrease in CKD progression and cardiovascular events, the lack of evidence should not be considered as evidence that such intervention could not be useful (table 35.4).

Obesity and Weight Loss

There are numerous studies in the literature about weight loss and its effects on BP, whether by dietary or pharmacological intervention or by bariatric surgery. There is also quite some evidence to support that obesity can affect the function of the kidney [52]. Nevertheless, there is no solid evidence supporting that weight loss has a beneficial effect on kidney disease progression in CKD patients. Regarding diabetic kidney disease, our current knowledge falls short on how lifestyle, medical, and surgical interventions can decrease CKD progression and whether there is a threshold weight loss required for benefit [53] (table 35.4).

Exercise

Exercise can lower BP, reportedly to a similar extent as a normal dose of an antihypertensive medication. However, adequately powered RCTs reporting the independent effects of exercise to slow down progression of kidney disease are lacking. One small trial ($n = 30$) randomized CKD patients to daily, 30-minute, aerobic exercise or usual care but failed to show that this slowed down progression of CKD [54]. Another observational study showed a 2.8% difference in eGFR decline between physically active people versus those who were sedentary [55]. This illustrates the need for adequately powered trials with sufficient follow-up to determine the potential benefits of exercise to slow down progression of CKD. Of note, exercise has been shown to decrease cardiovascular event rates in numerous other patient populations with cardiovascular risk.

A comprehensive review of lifestyle changes for the treatment of BP can be found elsewhere [56] (table 35.4).

ACEi and ARBs versus Other Medication in Hypertension in CKD

There is abundant literature about the actions of angiotensin II, besides intrinsic renal autoregulation, to maintain glomerular pressure when kidney perfusion pressure is decreased. This is achieved by preferential efferent arteriolar vasoconstriction. Conversely, blockade of angiotensin II action by ACE inhibition or AT1 receptor antagonists can decrease glomerular pressure by a decrease in BP, but also by a preferential efferent vasodilation. In addition, blockade of angiotensin II can decrease the glomerular ultrafiltration coefficient. Not surprisingly, it has been shown that angiotensin in many different models of kidney failure can decrease kidney damage and proteinuria more so than other agents, particularly calcium antagonists [57].

It is therefore rather surprising that clinical data on kidney protection of RAS inhibitors versus other agents is conflicting. There are several trial results suggesting that RAS inhibitors are more effective in decreasing progression of nondiabetic and diabetic proteinuric and nonproteinuric kidney disease compared to calcium channel blockers.

There are several considerations around this issue of effectiveness of RAS inhibitors versus other drugs. First,

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RAS inhibitors if dosed appropriately lead to an acute decrease in glomerular filtration, due to the mechanism explained above, and the absence of good autoregulation to offset the drop in BP in CKD patients. Administration of calcium antagonists has the opposite effect as they lead to an increase in glomerular filtration. If progression of CKD is studied, one should either study the changes in GFR after the initial changes in BP and glomerular filtration, or one should study the GFR after discontinuation of the study drugs. This is nicely illustrated in the report by Bakris, where he demonstrated a clear increase in GFR after discontinuation of the ACEi [58]. A related problem is that the exact same BP was not achieved in all studies. While in the IDNT study, for example, the difference was not more 2 mmHg [34], one cannot exclude that this explains (the absence) of differences between two study drugs. A third issue is whether other medications were allowed to be changed to control BP, which could introduce a confounder. Altogether the consensus seems to be that in diabetic and nondiabetic proteinuric kidney disease blockade of the RAS is the preferred first-line approach, whereas in nonproteinuric disease this is less conclusive.

Blood Pressure Target

No definitive conclusion can be reached about the best BP target for patients with CKD. On the one hand, there are no studies that have reached a solid conclusion about the best BP level to prevent the progression of proteinuric and nonproteinuric CKD. As mentioned, the SPRINT post hoc assessment of the effect of BP level on the progression of CKD did not reveal any benefit of lower BP goals [46]. That said, the trial was not powered to identify any benefit for specific etiologies of kidney failure. Similarly, the AASK trial could not demonstrate an additional benefit of intense versus standard treatment of BP in African Americans with nondiabetic hypertensive kidney injury [36]. The ACCORD-BP trial was unable to show this in patients with CKD stage 1–3B with diabetes [42]. Although there is no RCT comparing standard versus strict BP control to slow progression of CKD induced by IgA nephropathy, several observational studies support this [59, 60]. The Halt Progression of Polycystic Kidney Disease (HALT-PKD) trial compared strict versus standard BP control in autosomal dominant polycystic kidney disease (ADPKD) patients ($n = 558$). Intense BP control did not affect the primary outcome, percentage change in kidney volume, but it decreased the progression of CKD [61]. The clear observations from the SPRINT study have triggered a large dispute about the BP targets in patients with CKD. This has led to lowering of the target to 130/80 mmHg in the American College of Cardiology/American Heart Association guidelines for the management of HTN [62]. The most recent European Society of Hypertension/European Society of Cardiology guidelines now advise a target of 130–139 mmHg for systolic BP but do not mention a target for diastolic BP [63]. The debate about the right BP target is ongoing.

A Therapeutic Approach to Treatment of Hypertension in CKD

Although a physiology-based approach for more individually targeted treatment of HTN is not currently standard of care, such an approach may be considered in the management of patients who are identified as having truly resistant and difficult-to-control HTN. To effectively target a specific pathophysiological system, it is necessary to first demonstrate that the system is activated (using plasma hormone levels, physiologic measurements, or function tests). To date, key regulatory systems are not fully delineated and a comprehensive panel of "probes" is not yet available. With these limitations, assessment and targeting of several major regulatory pathways in HTN development is considered in this section.

Measurement of plasma renin activity or measuring the acute fall in BP after captopril administration may be used to predict BP response to RAS blockade [64]. Beyond the use of standard diuretic agents at standard doses, evaluation of volume status and urinary salt excretion could be used to assess a particular patient's salt-avidity and individual response to a diuretic agent and dosage. Evaluation of volume status and salt intake and excretion is not routinely performed and is technically difficult. Application of objective estimates of volume status using methods such as bioimpedance may be a consideration. Measurement of hemodynamic parameters and volume status using thoracic bio-impedance has been demonstrated to be an effective approach to improve BP control in several small trials [65]. A next important step would be to monitor salt intake and excretion by 24-hour urine sampling. Alternatively, a "salt calculator" has been developed, which consists of a survey of ~25 questions and provides an estimate of daily salt intake [66]. There is a body of evidence supporting the importance of increased activity of the SNS as one of the key factors in HTN in general and in hypertensive kidney disease in particular [21, 67]. Unfortunately, the activity of the SNS cannot be easily measured. Methods such as heart rate variability, plasma norepinephrine and catecholamines [68], and muscle sympathetic nerve activity [21] are not suitable for daily practice, and it is unclear whether these methods can reliably predict response to therapy.

BP responses to mineralocorticoid receptor inhibition reportedly are not related to plasma aldosterone concentrations or aldosterone-to-renin ratios in patients already treated for hypertension [69, 70]. Only in untreated patients was response to mineralocorticoid receptor inhibition linked

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to plasma aldosterone levels [71] and inversely to plasma renin activity [72]. Regarding patients with rHTN, plasma aldosterone, aldosterone-to-renin ratios, and 24-hour urine aldosterone levels were higher in those with rHTN versus controls [65]. Moreover, another study reported decreases in BP after addition of a low dose of spironolactone in patients with rHTN of 16.6/7.0, 23.9/9.7, and 26.0/10.7 mmHg at 1, 3, and 6 months after starting the drug [73].

Figure 35.2 illustrates an algorithm that can be followed to assess the effectiveness of targeted therapy for the

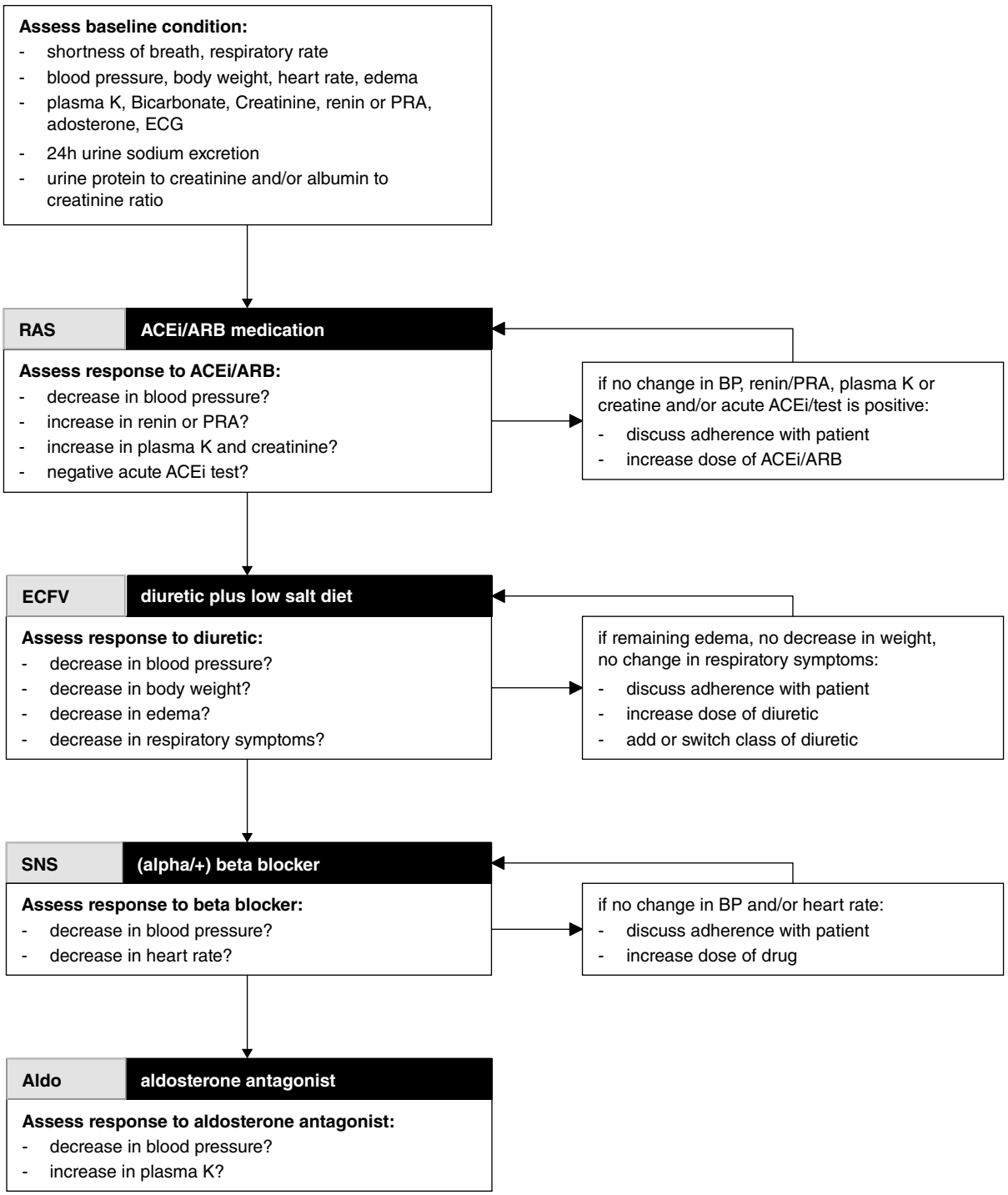

Figure 35.2 Physiology-based approach to treating hypertension in patients with CKD. Plasma K: plasm potassium concentration; PRA: plasma renin activity; ECG: electrocardiogram; RAS: renin-anigotensin system; ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; BP: blood pressure; ECFV: extracellular fluid volume; SNS: sympathetic nervous system; Aldo: aldosterone.

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physiological driving forces of BP as discussed. Until more evidence becomes available to support the use of such techniques in clinical practice, the proposed approaches can be considered in cases of individual patients with resistant and difficult-to-treat HTN to maximize targeted BP therapy.

Conclusion

Hypertension is not only prevalent in patients with CKD, it is also a key factor to control cardiovascular events in patients with CKD and to prevent progression of CKD itself. BP assessment is more complicated and needs special attention in patents with CKD. Since CKD by itself is an important determinant of disturbed BP control, secondary causes of HTN can easily be overlooked in this group. Inhibition of the RAS and volume control are key to BP management, next to lifestyle measures. Last but not least, BP treatment of the hypertensive CKD patient could benefit from a physiology-based approach.

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36

Chronic Kidney Disease-Mineral and Bone Disorder

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Introduction

Chronic kidney disease-mineral and bone disorder (CKD-MBD) is commonly encountered in the later stages of CKD. CKD-MBD is a systemic disorder manifest by abnormal calcium, phosphorus, parathyroid hormone (PTH), and vitamin D metabolism; abnormal bone turnover, mineralization, volume, growth, or strength; and vascular and soft tissue calcification. Clinical features of CKD-MBD, such as accelerated cardiovascular disease and skeletal pain and deformity, are associated with premature mortality and impaired health-related quality of life (QoL) and symptoms. Recipients of a kidney transplant experience changes in bone metabolism and bone quality related to drug effects, particularly corticosteroid therapy.

A range of treatments are used to correct the metabolic abnormalities observed with CKD-MBD. These include phosphate binding agents, vitamin D compounds and analogs, calcimimetics, dietary restriction, parathyroidectomy, and bisphosphonates. Although CKD-MBD is central to the care of moderate to severe CKD (stages 3b-5), much of the rationale for treatment has been based on biological reasoning rather than empiric evidence. The prevailing rationale for treatment has been that correcting abnormalities in bone and parathyroid metabolism can prevent complications (specifically, vascular calcification and skeletal fragility and deformity) and thereby improve patient survival and QoL. CKD-MBD is associated with bone demineralization and, more importantly, with skeletal symptoms and nonosseous calcification, including calcification of the vasculature. The latter is thought to contribute to the increased premature cardiovascular mortality that is observed in CKD.

The therapeutic approach to CKD-MBD that considers treatment of abnormal serum PTH and phosphorus levels, and that maintains serum calcium levels to prevent skeletal and cardiovascular morbidity, is based principally on observational studies. High-quality evidence arising from randomized controlled trials (RCTs) to inform clinical decision-making for CKD-MBD and transplant-related bone disease is limited. Treatment efficacy is generally evaluated based on surrogate biomarkers of bone metabolism, strength, and density, and serum biochemical markers. Current therapies for CKD-MBD rely on a combination of approaches, including hormone replacement where hormone deficiencies are present (e.g. 25-hydroxy-vitamin D and 1,25 dihydroxy-vitamin D) and suppression where excesses occur (e.g. PTH and phosphorus) and direct modulation of serum and/or whole-body phosphorus and calcium.

Treatment recommendations regarding CKD-MBD in CKD stages 1–4 have been based on expert opinion and the extrapolation of evidence from stage CKD 5D Table 36.1. There are also no well-designed clinical trials in CKD of any stage that have evaluated concurrent modulation of combination therapies (e.g. phosphate binders along with vitamin D and calcimimetics) on the long-term outcomes of mortality and nonbone-related morbidity, particularly cardiovascular complications. Short-term trials of combination therapy with vitamin D and cinacalcet are available for surrogate outcomes such as serum PTH.

Recent systematic reviews of trials have shown that there is often low or very low certainty that treatment of CKD-MBD makes a difference to the outcomes that directly impact on patients including cardiovascular complications,

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Table 36.1 Treatment for CKD-MBD.

Treatment	Recommendation	Certainty of evidence	Strength of recommendation
Vitamin D	We suggest vitamin D compounds can be used to lower serum parathyroid hormone levels for patients with CKD. Patients with CKD (any stage) may reasonably choose not to receive vitamin D compounds based on the very low certainty that treatment makes a difference to longer term outcomes, including quality of life, skeletal symptoms, growth and bone deformities, and cardiovascular morbidity and mortality.	*Low or very low* (mortality, cardiovascular events, skeletal symptoms, quality of life) *Moderate* (serum parathyroid hormone levels)	Weak [1, 2]
Calcimimetic therapy	We suggest calcimimetic agents can be used to lower serum parathyroid hormone levels or prevent parathyroidectomy for patients treated with dialysis. Patients with CKD (any stage) may reasonably choose not to receive calcimimetic therapy as treatment makes no difference to mortality and causes gastrointestinal side-effects and hypocalcemia.	*High* (mortality, hypocalcaemia, parathyroidectomy in patients treated with dialysis) *Moderate* (nausea in patients treated with dialysis) *Low or very low* (CKD stages 3–5)	Weak [3]
Phosphate binders	We suggest phosphate binder therapy may be used to lower serum phosphorus levels in patients with CKD. Patients with CKD (any stage) may reasonably choose not to receive phosphate binder therapy based on the very low certainty that treatment makes a difference to skeletal, cardiovascular, or quality of life outcomes. The specific choice of phosphate binder may be determined by patient preferences for avoidance of specific adverse effects.	*Moderate* (gastrointestinal side-effects and hypercalcemia) *Low or very low* (mortality, cardiovascular events, skeletal symptoms, parathyroidectomy, quality of life)	Weak [4, 5]
Dietary restrictions	We suggest dietary phosphorus restriction may be used in patients with CKD to lower serum phosphorus levels. Patients with CKD may reasonably choose not to restrict dietary phosphorus based on the very low certainty that dietary modification makes any difference to mortality, cardiovascular events, or skeletal complications.	*Very low*	Weak [6]
Serum biochemical targets	We suggest that treatment of mineral and bone disorder is not guided by specific serum levels of parathyroid hormone, phosphorus, or calcium by phosphorus product based on the very low certainty that this approach makes a difference to longer term outcomes, including quality of life, skeletal symptoms, growth and bone deformities, and cardiovascular complications and mortality.	*Very low*	Weak [7]
Transplant bone disease	We suggest that bisphosphonates may be used to prevent fracture and bone pain. Patients with a kidney transplant may reasonably choose not to receive bisphosphonate therapy based on the low certainty that treatment makes any difference to skeletal complications and low certainty of safety information.	*Low*	Weak [8]

GRADE assessment of the certainty of the evidence [9]: High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different* is low. Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different* is moderate. Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different* is high. Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different* is very high. **Substantially different = a large enough difference that it might affect decision-making*.

skeletal symptoms and deformity, growth in children, and QoL. Based on these findings, the choice of treatment should be based on patient preferences for improvement of specific outcomes and the avoidance of side effects, together with treatment availability and cost.

This chapter examines the evidence for management of CKD-MBD in adults, including transplant-related bone disease.

Definition

CKD-MBD is a systemic disorder of mineral and bone metabolism caused by impaired kidney function with one or more of the following abnormalities: dysregulated calcium, phosphorus, PTH, or vitamin D metabolism; altered bone turnover, mineralization, volume, linear growth or strength; or vascular or other soft tissue calcification [10].

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CKD-MBD usually develops over several years, with an asymptomatic phase that is manifest by hormone and serum abnormalities, including progressive increases in serum phosphorus and PTH. As the condition becomes symptomatic, patients can experience bone fragility causing pain or fracture, disability and impaired QoL, and vascular and valvular calcification causing cardiovascular complications, hospital admissions, and premature death.

In clinical practice during the 1980s and 1990s, disorders of bone and mineral metabolism caused by CKD were considered to be largely limited to bone abnormalities, hence the term "renal osteodystrophy." Renal osteodystrophy describes the pathological changes in bone morphology associated with CKD and is characterized by bone histomorphometry changes based on bone biopsy. Renal osteodystrophy includes a range of bone disorders including osteitis fibrosis cystica (high turnover with mineralization defect and normal bone volume), adynamic bone disease (low turnover with normal mineralization and low or normal bone volume), osteomalacia (low turnover with abnormal mineralization and low to medium bone volume), and mixed uremic osteodystrophy (high turnover with mineralization defect and normal bone volume).

The broader term, CKD-MBD, was developed by a consensus workshop in 2005 to recognize the diverse range of systemic manifestations of altered mineral metabolism [11]. As a result of this conference, the term renal osteodystrophy was recommended as a term used exclusively to define alterations in bone morphology associated with CKD, with reporting on histomorphometry based on a unified classification system including parameters of bone turnover, mineralization, and volume (TMV). The term CKD-MBD was recommended to describe the broader clinical syndrome manifest by abnormal bone and mineral metabolism and/or skeletal calcification.

For each patient, the clinical manifestations of CKD-MBD are varied and change over time. The variable phenotypic expression of CKD-MBD leads to the challenge of identifying and using a single and reproducible measure to define CKD-MBD and assess response to treatment.

Epidemiology

The heterogeneity in clinical and biochemical abnormalities of CKD-MBD makes it difficult to determine its exact prevalence in patients with CKD. The prevalence also depends both on the clinical characteristic used to identify the presence of the syndrome and the stage and duration of CKD.

Serum calcium and phosphorus levels tend to remain within normal physiological limits (>2.1 mmol/l and <1.5 mmol/l, respectively) until the glomerular filtration rate (GFR) is below 30 ml/min [12]. Approximately 40% of patients with a GFR <20 ml/min experience abnormal serum phosphorus and levels while 15–20% of such patients experience abnormal serum calcium levels. Serum PTH levels increase with decreasing GFR levels. High serum levels (>7.4 pmol/l) are present in 12% of those with GFR>80 ml/min, 17% of those with GFR 70 and 79 ml/min, 21% of those with GFR between 60 and 69 ml/min, and 56% of those with GFR <60 ml/min [12]. Serum 1,25-dihydroxy-vitamin D_3 concentrations tend to increase in parallel with decreases in GFR, with levels of 22 pg/ml experienced by approximately half of patients with a GFR between 20 and 29 ml/min.

Determining the prevalence of bone morphology changes caused by CKD is more challenging to assess than serum biomarkers due to the invasive nature of the bone biopsy, potential coexistence of osteopenia or osteoporosis in older patients, and the range of treatments used to manage CKD-MBD. Abnormal bone metabolism is observed in nearly all patients with CKD stage 5D (requiring dialysis) and most patients with CKD stages 3–5. Adynamic bone disease, in which low bone turnover with normal mineralization occurs (with diminished osteoblast activity, bone formation, and activation) is present in 10–71% of patients with CKD stage 5D and 5–49% of patients with CKD stages 3–4 [13]. Due to secular trends in treatment of CKD-MBD and increasing comorbidity associated with CKD, the prevalence of adynamic bone disease appears to be increasing.

Medial vascular calcification is highly prevalent in patients with CKD and inversely correlates with GFR [14]. In young patients treated with dialysis, coronary artery calcification, measured by electron beam computed tomography, was present in 80% of patients between 20 and 30 years old, and nearly doubled over a period of 20 months [15]. In a small study in 48 patients with a GFR between 17 and 55 ml/min, 90% of patients demonstrated aortic vascular calcification, suggesting the majority of patients with CKD stages 3–5 have arterial calcific changes [16].

Recipients of a kidney transplant lose bone rapidly and early after transplantation from body sites rich in trabecular bone [17]. Bone mineral density may decline by 4–10% in the first 6 months, with further decreases of 0.4–4.5% between 6 and 12 months [18, 19]. Devolution of parathyroid gland overactivity decreases after transplantation, but PTH levels may remain elevated in 45% of kidney transplantation recipients for up to 2 years [20]. Bone histomorphometry shows increased trabecular separation and reduced number, delayed mineralization and lower mineralizing surface, and higher osteoid surfaces with lower bone volume [21].

This figure 36.1 illustrates some of the complex relationships between calcium, phosphorus, vitamin D, and PTH that determine normal mineral metabolism and some of the

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ways in which these relationships may be altered in CKD leading to the development of CKD-MBD. Two processes mediate the early events in the pathogenesis of CKD-MBD in early CKD: the renal and systemic responses to excess phosphorus and the fall in active 1,25 dihydroxy-vitamin D levels. The number of functioning nephron units declines as kidney function worsens. The maintenance of normal serum phosphorus levels in the presence of CKD is dependent on an increase in phosphate excretion per nephron. High PTH and low active vitamin D levels inhibit tubular phosphate transport by decreasing sodium-dependent phosphate cotransporter activity. Fibroblast growth factor (FGF)-23 and the FGF-23 FGFR-Klotho complex may be important modulators of renal phosphate excretion. In addition, FGF-23 appears to reduce $1,25(OH)_2$ vitamin D in part by decreased 1-α-hydroxylase activity. The fall in 1-α-hydroxylase activity in CKD is most likely secondary to multiple mechanisms. Active vitamin D is also reduced in many patients because of insufficient 25 hydroxyvitamin D. Low levels of active vitamin D reduce calcium absorption from the gastrointestinal tract and stimulate secretion of PTH. Additionally, low calcium levels stimulate PTH secretion. Consequently, calcium levels are partially restored by release of calcium from the bone. Excess PTH, hyperphosphatemia, and vitamin D deficiency each appear to contribute to the development of the systemic and vascular manifestations of CKD-MBD.

Pathophysiology

Renal osteodystrophy was recognized as a significant and progressive disease in patients with CKD stage 5 soon after effective renal replacement therapy became generally available in North America, Europe, and Asia. The disease state was recognized principally as a demineralizing and debilitating bone disease leading to gross skeletal deformation, hypocalcemia, and hyperphosphatemia. It was observed to be more prevalent in patients with prolonged kidney failure, and especially among those with chronic diseases of the renal tubulo-interstitium [22]. Bone biopsy studies demonstrated that the degree of disordered bone architecture was associated directly with the degree of hyperparathyroidism and that the latter correlated in some studies to 25(OH)-vitamin D deficiency or to $1,25(OH)_2$-vitamin D deficiency [23–26].

Abnormalities of bone and mineral metabolism start to occur in CKD stages 2 and 3 when the GFR is between 40 and 70 ml/min. Even before clinical changes are observed in serum phosphorus levels, injury to kidney tissue stimulates circulating signals that modify osteocyte function. An overview of the pathogenesis of CKD-MBD is shown in Figure 36.1.

A progressive increase in fibroblast growth factor 23 (FGF23) occurs as GFR falls due to increased secretion by

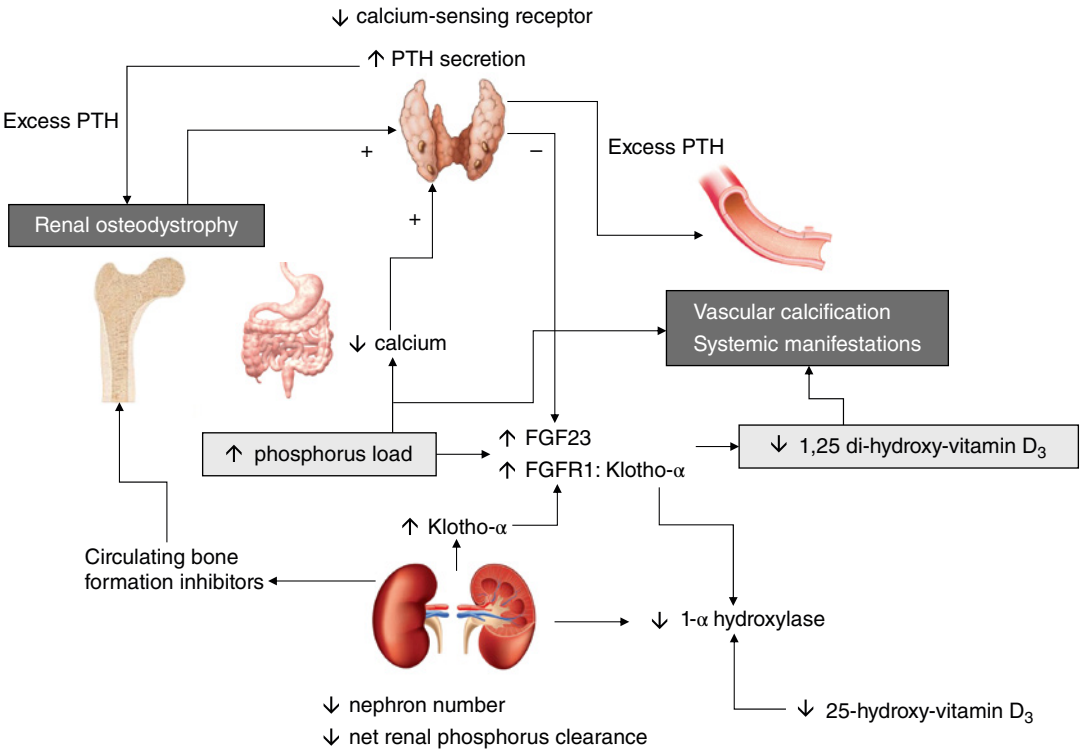

Figure 36.1 Pathogenesis of secondary hyperparathyroidism and CKD-MBD.

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osteocytes and osteoblasts, loss of secretory inhibition, and impaired renal excretion [27]. FGF23 acts together with a coreceptor, the transmembrane protein Klotho-α, to suppress PTH gene expression and secretion [28]. Klotho-α is also expressed in the proximal renal tubule, acting to regulate tubular phosphorus transport, together with modulation of 1α-hydroxylase and 24-hydroxylase, involved in the activation steps of vitamin D_3 [29]. The maintenance of normal serum phosphorus levels in the presence of CKD is dependent on an increase in the fraction of filtered phosphate reabsorbed per nephron. High PTH and low active vitamin D levels inhibit tubular phosphate transport by decreasing sodium-dependent phosphate cotransporter activity and increasing phosphate excretion per nephron. In addition, FGF-23 appears to reduce $1,25(OH)_2$ vitamin D_3 in part via decreased 1-α-hydroxylase activity.

The fall in 1-α-hydroxylase activity in CKD is most likely secondary to multiple mechanisms. Active vitamin D is lower in many patients because of insufficient 25-hydroxy-vitamin D. 25-hydroxy-vitamin D (calcidiol) is the substrate for 1-α hydroxylase action and can be reduced in CKD due to lower sun exposures, lower skin synthesis of cholecalciferol with uremic-pigmentation, and dietary restrictions. Low levels of active vitamin D (1,25-dihydroxy-vitamin D_3) result in reduced calcium absorption through the gastrointestinal tract and stimulate secretion of PTH. Additionally, low serum calcium levels lead to increases in PTH secretion through exocytosis due to lower activation of the calcium-sensing receptor. In response, serum calcium levels are partially restored by release of calcium from the bone.

The progressive decrease in 1,25-hydroxylation of vitamin D_3 through decreasing 1-α hydroxylase activity in kidney tissue, mediated in part by the counter-regulatory actions of FGF-23, is an important factor in the development of CKD-MBD [30]. Decreasing 1,25-hydroxy-vitamin D_3 levels and the consequent hypocalcemia are key stimulants of PTH secretion. A complex interplay between vitamin D deficiencies, low serum calcium, high serum phosphorus, elevated FGF-23 levels which reduce calcitriol activity, together with impaired intestinal absorption of dietary and supplemental vitamin D, and altered dietary patterns caused by uremia, are the hallmarks of CKD-MBD.

Abnormalities in bone due to CKD include changes in bone turnover, mineralization, and volume (Figure 36.2), leading to pain, fracture, and deformity.

Excessive circulating PTH increases bone turnover. Disordered osteoblast function results in impaired collagen release and the generation of woven bone structure. Fibrosis occurs in the peritrabecular and marrow contours due to

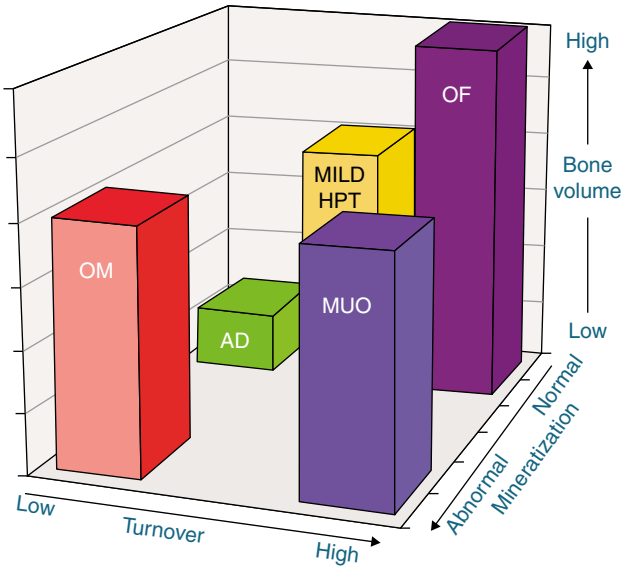

Figure 36.2 Changes in bone architecture and metabolism in CKD-MBD. AD, adynamic bone disease. HPT, hyperparathyroidism. MUO, mixed uremic osteodystrophy. OM, osteomalacia. (Permissions needed from [11]). *Source:* Moe S et al. [11]. © 2006, Elsevier.

collagen deposition from fibroblastic osteoprogenitors. Osteoid, the nonmineralized structure within bone, is expanded, resulting in loss of the usual three-dimensional structure of bone architecture. Mineralization of bone is accelerated, leading to altered bone strength and form. This process of abnormal and increased bone osteoid generation and mineralization is known as high bone turnover renal osteodystrophy (or osteitis fibrosa). Low-bone turnover disease is marked by reduced bone turnover, suppressed bone formation, and impaired bone mineralization, leading to accumulated nonmineralized bone matrix and increased osteoid volume. A mixed osteodystrophy results from high PTH levels together with impaired mineralization. Bone formation is variable and can be high or low. Increased number and activity of osteoclasts is seen together with accumulated woven osteoid, and variable mineralization depending on the presence of woven or lamellar bone. Vascular smooth muscle cells are located in the media of vessel walls and contract to regulate vascular tone.

In the presence of uremic serum and inorganic phosphate, high glucose, oxidized lipids, and cytokines, vascular smooth muscle cells can dedifferentiate into osteocytic-like cells. This osteogenic phenotype increases expression of bone-forming transcription factors and matrix proteins [31]. The transformed vascular smooth muscle cells secrete collagen and noncollagenous proteins within the vessel intima and media. Incorporation of calcium and phosphorus within matrix vesicles initiates mineralization, leading to vascular calcification [32].

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Figure 36.2 shows the prevalence of combinations of bone volume, turnover and mineralization. Clusters of characteristics can identify commonly encountered discrete pathological abnormalities that occur in CKD-MBD. For example, high bone volume, with normal mineralization and high bone turnover, characterizes osteitis fibrosa (OF) or advanced hyperparathyroid bone disease.

Transplant bone disease is characterized by pre-existing CKD-MBD, persistent hyperparathyroidism despite normalization of kidney function, hypovitaminosis D, and immunosuppression effects, particularly glucocorticoid treatment [33].

Diagnostic Tests

As CKD-MBD has protean manifestations that can be specific to the individual patients and vary based on severity of kidney disease and treatment, none of the diagnostic tests used for clinical decision-making measure all aspects of CKD-MBD. The diagnostic approach can be based on specific clinical probability of abnormalities and as a guide to treatment. The diagnostic tests to evaluate CKD-MBD are outlined in Table 36.2. In general, diagnosis and assessment involve evaluation of biochemical abnormalities and bone and vascular involvement. To date, there are no systematic summaries of diagnostic test performances of clinical methods used to evaluate CKD-MBD.

Biochemical Abnormalities

Clinical practice guidelines recommend biochemical markers including serum PTH, calcium, phosphorus, and bone-specific alkaline phosphatase to guide management and provide indirect information about high and low bone turnover [10]. Biochemical markers are not diagnostic of the clinical complications of CKD-MBD (bone disease, vascular occlusion, and symptoms) but are simple to obtain and can indicate responses to therapeutic interventions.

Serum PTH

Serum PTH rises progressively as kidney function declines and is often elevated above the normal range (1.1–7.4 pmol/l) in stages 3 and 4 CKD. PTH is the most commonly used biochemical marker to indicate likely bone turnover. A specific target range has not been identified at which clinical outcomes are reduced, and clinical practice guidelines suggest a broad range of appropriate values, consistent with this lack of evidence. High PTH levels (>91.2 pmol/l) combined with complications including refractory itch, skeletal pain or malformation, persistent hypercalcemia, and extraskeletal calcification may prompt consideration of surgical parathyroidectomy. Serum PTH levels may be poorly predictive of bone histological changes, although values at the extremes of the range can be specific for high and low bone turnover. In a retrospective study, the best cut-point to discriminate low from high bone turnover was an intact PTH <11.8 pmol/l while the best cut-point to discriminate high from low bone turnover was >36 pmol/l [39]. There may be some utility in serial measures of PTH to detect a rising concentration that might prompt identification of reversible causes including high dietary phosphorus, low dialysis dose, or vitamin D deficiency, or indicate the need to consider parathyroidectomy if symptoms arise.

Serum Phosphorus, Calcium, and Vitamin D

Serum phosphorus and calcium are commonly measured at regular intervals in clinical care. The serum levels are not diagnostic of a specific process and should be interpreted in the context of other findings (including symptoms, treatment, and serum PTH levels). Measurement of 25-hydroxy-vitamin D_3 may identify vitamin D deficiency (<50 nmol/l) or insufficiency (50–75 nmol/l). Circulating levels do not necessarily correlate with kidney function.

Bone

Bone tissue in CKD-MBD has abnormal turnover (balance between production and resorption), mineralization, and volume. A variety of measures have been used to assess for renal osteodystrophy and vary in terms of specificity, the range of information provided about bone turnover, mineralization, and volume, and the availability of diagnostic tests within routine clinical practice.

Bone-specific Alkaline Phosphatase

Alkaline phosphatase (ALP) circulates as several isoforms, including liver-specific and bone-specific ALP. Nearly all (95%) of circulating ALP is either bone- or liver-derived in equal ratios. Bone-specific ALP above 20 ng/ml has high sensitivity and specificity for identifying patients with high bone turnover and excluding those with low bone turnover [36]. Total ALP (including liver isoforms) has lower specificity for high (specificity 90%) and low (specificity 50%) bone turnover at a cut-point of 200 IU/l.

Biomarkers of Collagen and Bone Metabolism and Activity

Serum biomarkers such as osteocalcin, osteoprotegerin, TRAP-5b, pyridinoline, deoxypyridinoline, procollagen type 1 amino-terminal extension peptides, and C-terminal

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Table 36.2 Summary of diagnostic tests in CKD-MBD.

Test	What does it measure?	Comments
Biochemical		
Parathyroid hormone	• Measures circulating intact parathyroid hormone • Normal 1.1–7.4 pmol/l • PTH fragments accumulate in CKD and may interfere with some assays	• Optimal level unknown in CKD • Rising level can prompt for assessment of high phosphate levels or intake, hypocalcemia, and/or vitamin D deficiency • Low levels may indicate risk of low bone turnover • Serum PTH levels poorly predict bone histology • High PTH levels together with symptoms (high serum calcium, symptomatic bone disease, refractory pruritus, extraskeletal calcification or calciphylaxis, unexplained myopathy) may prompt consideration of surgical parathyroidectomy
Calcium	• Measures circulating calcium concentrations but not ionized levels • Needs adjustment for serum albumin • Not indicative of total body calcium burden	• Can be low due to decreased 1,25-di-hydroxy-vitamin D_3 levels, phosphatemia, and blunted bone response to PTH • Can be elevated secondary to treatment and/or tertiary hyperparathyroidism • Low levels associated with tetany and cardiac arrhythmias; high levels associated with kidney stones, mood disorders, acute kidney injury, and consitpation
Phosphorus	• Measures circulating serum phosphorus concentrations. • Influenced by food intake, adherence to and timing of medication, and interval from last dialysis • Serial measures most appropriate to guide therapy	• Optimal level unknown in CKD • Interpretation in context of other biomarkers and patient's treatment and symptomatic state is appropriate
25-hydroxy-vitamin D_3	• Identifies vitamin D deficiency (<50 nmol/l) or insufficiency (50–75 nmol/l) [34]	• Not directly correlated with GFR • 10–50% of patients with CKD stages 3 and 4% have levels >75 nmol/l • Can guide therapeutic replacement although high certainty evidence of improved clinical outcomes not available
Bone		
Alkaline phosphatase	• 95% of serum alkaline phosphatase (ALP) in healthy adults is either bone ALP or liver ALP isoforms in approximately equal parts [35] • Testing for bone-specific ALP isoform can provide predictive information for bone histology and activity	• Lower biological variability than PTH • Markedly high or low levels of bone-specific may predict bone turnover • Elevated bone-specific ALP (20 μg/l) and PTH (>22 pmol/l) has 100% sensitivity and 80% specificity for high turnover bone disease [36] • Combining bone-specific ALP <20 μg/l and PTH <22 pmol/l provides 100% sensitivity and 100% specificity for low turnover bone disease [36]
Bone-derived turnover markers of collagen synthesis and breakdown	• Includes markers of synthesis (procollagen type I C-terminal propeptide) and breakdown (type I collagen cross-linked telopeptide, pyridinoline, deoxypyridinoline)	• Uncertain diagnostic utility in CKD • Variable renal clearances and undefined reference ranges for CKD mean these tests are not currently recommended in routine diagnostic work-up for CKD-MBD

(*Continued*)

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Table 36.2 (Continued)

Test	What does it measure?	Comments
Bone biopsy	• Measures bone microarchitecture, turnover, and mineralization • Considered gold-standard for assessment of renal osteodystrophy	• Invasive, requires expertise to perform, process, and interpret; rarely performed in clinical care • Limited usefulness for monitoring treatment response due to invasiveness
Dual-energy X-ray absorptiometry (DXA)	• Measures bone mineral density (BMD) in grams per square centimeter	• Inexpensive, noninvasive, and low radiation exposure • Limited information about bone quality or turnover • Low bone mineral density may predict fracture in any stage of CKD [37, 38]
High-resolution peripheral quantitative computed tomography (HR-pQCT)	• Measures three-dimensional microstructure of cortical and trabecular bone to generate microstructural analysis • Evaluates bone mechanical competence • Evaluates distal tibia and radius • Measures volumetric bone mineral density	• Low radiation • Requires specific scanner, not available in many clinical settings • Limited standardized reference data • Limited evidence of validation against bone histomorphometry • Not in routine clinical care
High-resolution magnetic resonance imaging (HR-MRI)	• Measures bone microarchitecture • Evaluates distal tibia, radius, femur	• No ionizing radiation • Routine scanning equipment • Limited evidence of validation against bone histomorphometry • Complex post-processing analysis • Not in routine clinical care
Cardiovascular		
Lateral X-ray lumbar abdominal aorta	• Semi-quantitative estimation of calcification of abdominal aorta	• Sensitivity 62%, specificity 78% for coronary artery calcification if X-ray score >7 • Simplicity
Computed tomography	• Electron bean (EBCT) and multislice (MSCT) • Coronary artery calcification measured as Agatston score is calculated as the product of a calcified plaque area by a coefficient related to the peak CT density measured within the same plaque	• Radiation • Not able to differentiate between intimal and medial calification • Limited information about severity of obstructive coronary artery disease
Echocardiogram	• Identification of valvular abnormalities	• Readily available • Functional cardiac information • No radiation

crosslinks have no role in clinical care due to their lack of diagnostic evidence and renal elimination, leading to difficult interpretation of their diagnostic test performance in the presence of CKD [11].

Bone Structure and Quality

Diagnostic tests for renal osteodystrophy would ideally examine the essential properties of bone: strength for load-bearing, flexibility to absorb energy, compression, and tension without fracture, and volume and weight to facilitate mobility [40]. Assessing the quality of bone structure to bear mechanical load without injury is limited as diagnostic tests measure indirect markers of bone metabolism or turnover, density, or structural composition. Routinely used diagnostic approaches for CKD-MBD would optimally identify specific functional or structural bone abnormalities that can be ameliorated by therapy to prevent adverse patient outcomes. However, not all fractures or bone symptoms have the same pathogenesis and CKD-MBD is characterized by highly heterogeneous changes to bone density, architecture, mineralization, and volume. Standard diagnostic approaches to fracture risk secondary to osteoporosis may have different diagnostic utility in the present of CKD.

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In this section, the diagnostic strategies to examine bone density and bone structure and quality are discussed.

Bone Imaging

Bone Mineral Density

A key purpose of diagnostic evaluation of renal bone disease is to predict and guide management based on patient-relevant outcomes, including risks of skeletal deformity, loss of height, bone pain, and low trauma fracture. Assessing bone mineral density (BMD) is recommended by the United States Preventive Task Force [41] as a component of screening for osteoporosis in women older than 65 years and younger women at higher risk of fracture. The role of BMD assessment to guide management in CKD-MBD is more uncertain.

Hyperparathyroidism may lead to sclerosis and thickening of trabecular bone (and increased BMD) with concurrent accelerated resorption of cortical bone (with reduced BMD). Consequently, BMD may poorly predict fracture risk and lead to administration of anti-osteoporotic therapy that adversely impacts on bone metabolism.

A previous consensus workshop on the definition and evaluation of CKD-MBD in 2006 cited a study in 70 patients treated with hemodialysis, in which mid-radius but not femoral neck and lumbar spine BMD was decreased and correlated with time on dialysis [42]. While BMD at all sites (mid-radius, femoral neck, lumbar) was negatively correlated with bone-specific ALP and serum-intact PTH, there was no association with fracture occurrence, suggesting BMD may have limited utility in CKD-MBD.

BMD measurement using dual-energy X-ray absorptiometry (DXA) is suggested by the 2017 updated Kidney Disease: Improving Global Outcomes (KDIGO) guidelines for patients in whom knowledge of fracture risk will inform decision-making [10]. This is consistent with findings in a longitudinal cohort study involving 131 patients with CKD stage 5 treated with hemodialysis [43]. A BMD T-score ≤−2.5 at the total hip had a sensitivity of 88.5% and specificity of 65.6% for incident low trauma fractures or morphometric spine fractures, while the diagnostic test performance of lumbar spine BMD was somewhat lower (81.3 and 68.6%). In a second study of 485 hemodialyzed patients who were followed for 5 years for radiographic spine or any clinical fracture, the sensitivity and specificity for any fracture was highest for total hip BMD T score ≤−2.7 (66.7% and 84.9%) for patients with a serum PTH <23.3 pmol/l, and had lower predictive utility in those patients with a serum PTH above the same cut-point [37].

There are no high-quality studies evaluating the performance of DXA for BMD to predict clinical bone outcomes after kidney transplantation.

Quantitative Computed Tomography

In addition to DXA, BMD can be quantified using quantitative computed tomography (QCT), which provides a volumetric assessment of bone density, differentiates between cortical and trabecular bone, and is less prone to interference from bone deformity and overlying nonosseus calcification. QCT can assess BMD at the hip and vertebra peripheral body sites, and involves high radiation exposure. Peripheral QCT (pQCT) is an application of QCT that can evaluate BMD at distal sites, such as the radius or tibia.

High-resolution (HR) peripheral QCT (HR-pQCT) is similar to QCT, although higher spatial resolution allows HR-pQCT to measure BMD in the distal extremities (specifically the radius and tibia). In patients with stage 5D, HR-pQCT at the radius measuring cortical bone structures (area, density, and thickness) provided the highest AUCs (0.73, 0.72, and 0.72, respectively) to predict any incident radiological spinal or low trauma fracture [43]. The predictive value of trabecular bone parameters derived from HR-pQCT was lower than for cortical bone. In a study comparing vertebral bone density obtained by QCT with bone histomorphometry in 26 patients treated with hemodialysis, vertebral BMD by QCT was correlated with trabecular bone volume, while QCT for vertebral BMD had an AUC of 0.76 for bone volume by bone biopsy [44].

In addition to measurement of BMD in distal sites, HR-pQCT can provide information about bone microstructure including cortical density, area, and thickness, and trabecular number and architecture. In 91 patients with CKD (32 with fracture and 59 without fracture), HR-pQCT of the radius in those with fracture demonstrated lower cortical area and thickness, and lower trabecular number and greater trabecular separation [45]. The discrimination for fracture by HR-pQCT parameters varied by duration of CKD.

Magnetic Resonance Imaging

High-resolution MRI (HR-MRI) and micro-MRI provide 3D information of bone morphology and trabecular structures at peripheral body regions and avoids the need for ionizing radiation [46]. These tools may provide noninvasive evaluation of renal osteodystrophy, but remain largely limited to research settings.

Bone Biopsy

The bone biopsy remains the gold standard for detailed information about bone metabolism, but remains limited in clinical practice due to the invasive nature of the procedure and the expertise required to conduct, process, and analyze the information provided. The bone biopsy can allow the direct visualization of bone to evaluate bone turnover, mineralization, and volume, according to

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a standardized nomenclature based on these components (turnover/mineralization/volume; TMV) [11]. Unlike biochemical markers, bone biopsy can distinguish high turnover bone disease from other forms of bone disease, including mixed osteodystrophy, low bone turnover (adynamic bone disease, osteomalacia), and bone pathologies caused by specific etiologies.

The bone biopsy has not been recommended for routine care, but may assist specific management in the presence of inconsistency among diagnostic tests, unexplained fracture or bone pain, severe progressive vascular calcification, unexplained hypercalcemia, possible aluminum toxicity, definitive histological diagnosis before parathyroidectomy, and prior to bisphosphonate treatment.

Bone biopsy after kidney transplantation may identify patients who have low bone turnover, for whom antiresorptive therapies may increase risks of complications, although there are no studies evaluating the diagnostic test performance of bone histomorphometry in the setting of kidney transplantation [33].

Fracture Risk Assessment

The Fracture Risk Assessment Tool (FRAX) incorporates demographic variables (age, sex), clinical factors (weight, height), and risk factors for factor (previous facture, smoking, glucocorticoids, rheumatoid arthritis, alcohol intake, secondary osteoporosis) with or without BMD to estimate a ten-year probability of fracture [47].

Evidence supporting FRAX as a predictive tool in CKD is limited. The performance of the FRAX score has been tested in a Canadian multicenter study of patients over 40 years with CKD stage 3 [48]. FRAX with BMD has moderate–low discriminatory power to predict fracture (AUC 0.69). In a study involving recipients 1-year on average after kidney transplantation, the FRAX score with bone mineral density had limited predictive utility for major fracture (AUC 0.62) [49].

Vascular Calcification

Diagnostic tests for vascular calcification in patients with CKD include assessment for abdominal aortic and valvular calcification.

Plain Radiography

Abdominal aortic calcification can be identified by a lateral abdominal radiograph (to avoid the overlay of the aorta and the vertebral structures). X-rays can be assessed for the presence of vascular calcification. Plain radiography is a simpler, cheaper test for calcification that limits radiation exposure compared with computed tomography. In addition, semiquantitative measures of severity can be applied to provide a calcification score (range 0–24) [50]. In a study of 275 adults treated with hemodialysis, 77.8% had abdominal aortic calcification with a median score of 6 [51]. Evidence for the diagnostic utility of abdominal X-ray to predict clinically relevant disease in CKD is sparse. In 90 patients treated with hemodialysis, a cut-off vascular calcification score of 6.5 on abdominal radiography had a sensitivity of 85% and specificity of 57% for coronary artery disease [52].

Computed Tomography

Computed tomography (electron beam [Electron Beam Computed Tomography] or multislice [Multi-slice computed tomography]) provides quantitative assessment of coronary artery calcification. The degree of coronary artery calcification can be calculated using the Agatston score, calculated by multiplying the area of each calcified lesion by the pixel intensity of the lesion [53]. The scores for each lesion are then summed to provide an overall score, reflecting burden and intensity of calcification. Calcification scores in adults of 0–10, 11–100, >100, and >400 represent low, intermediate, progression from intermediate to high, and highest risk, respectively [54]. Patients treated with dialysis have coronary artery calcification scores 10-fold higher (approximately 4000 on average) than age-matched patients [55].

In a study of young patients with CKD stage 5 (ages 7 to 30 years), nearly all (88%) patients older than 20 years of age had evidence of coronary calcification with EBCT, compared with 5% of similarly aged people without CKD stage 5 [15]. In a small study in 29 patients with CKD stage 5, a CT-based coronary artery calcium score >500 had sensitivity and specificity of 50% and 80% for detecting coronary artery stenosis ≥50% luminal narrowing on percutaneous angiography. This suggests that CT calcification has a low detection rate for coronary artery stenosis, but may have moderate test performance for exclusion of coronary artery narrowing [56]. The current role of coronary artery calcification scores to detect luminal coronary artery occlusion or for clinical-decision making is uncertain [57].

Echocardiography

There are limited data on the diagnostic utility of echocardiography for clinical decision-making about cardiac valvular calcification specific to the setting of CKD.

Prognosis

Skeletal Complications (Fracture, Pain, Deformity)

Several large-scale studies have demonstrated increased risks of fracture for patients with CKD stage 5D. Hip fractures measured using ICD-9 codes occur at an incidence of

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8 per 1000 person-years for men and 14 per 1000 person-years for women, suggesting a relative risk approximately fourfold that of the general population [58]. Prior kidney transplantation increases fracture risk, which becomes attenuated over time after surgery, while among transplant recipients fracture risk is higher among those with a prolonged duration of dialysis prior to transplantation. The incidence of fracture is higher among those with low or high serum PTH levels and for those receiving psychoactive or corticosteroid medications [59, 60].

In nearly two million community-living adults, and using diagnostic and procedure codes to evaluate fracture risk during 4.4 years of follow-up, there appears to be no increased risk of hip, wrist, or vertebral fracture among those with an estimated GFR below 60 ml/min per 1.73 m^2 [61]. It is possible that evidence of higher fracture risk associated with CKD is due to confounding by comorbidity, including inflammation and BMD [62].

Risks of fracture after kidney transplantation are highly heterogeneous, ranging from 3 to 100 fractures for every 1000 person-years [63]. Differences between studies are likely to relate to study population differences, type of fracture, and duration of dialysis before transplantation. Overall, the 10-year cumulative incidence of hip fracture for kidney transplantation is 1.7%, while the 3-year nonvertebral fracture incidence (1.6%) may be lower than the general population with a previous nonvertebral fracture (2.3%) [64].

The incidence of bone pain and skeletal deformity with CKD is less frequently reported than fracture, likely due to the availability of diagnostic and procedural codes to capture fracture-related events for longitudinal analyses compared with the challenge of systematic collection of symptoms and patient-reported outcome measures. In a community cross-sectional study among 1118 patients with CKD, bone and joint pain was the most frequently experienced symptom [65], although this has not been a consistent finding in the literature [66, 67]. Similarly, there are insufficient systematic data recorded on skeletal pain or deformity for recipients of a kidney transplant.

Mortality and Cardiovascular Events

The protean manifestations of CKD-MBD, including biochemical abnormalities, vascular calcification, and fracture, are associated with mortality, hospitalization, and cardiovascular events. The rationale for therapeutic control of serum PTH and phosphorus levels has been, in part, evidence of the "dose-dependent" association between higher serum phosphorus and PTH concentrations with all-cause mortality, as demonstrated in two seminal studies by Block et al. [68, 69]. However, in a systematic review of 47 cohort studies, while there is evidence that the risk of death increases by 18% for every 1 mg/dl increase in serum phosphorus (0.32 mmol/l), there is little evidence that serum levels of calcium and PTH are associated with all-cause or cardiovascular mortality [7]. Similarly, there are no robust cohort data to show that alterations in serum concentrations over time are linked to clinical outcomes, or that therapeutic modulation of serum phosphorus levels improve clinical outcomes.

Bone-related abnormalities including altered bone mineral density, fracture, high or low bone turnover diseases and extra-osseus calcification are all associated with worse clinical outcomes, including cardiovascular events, hospitalization, and death. As with serum parameters, evidence that treatment modification or prevention improves QoL or survival is awaited, while associations with clinical outcomes may represent confounding due to kidney function and comorbidity that cannot be accounted for by statistical adjustment [70].

Treatment

Historically, treatment of CKD-MBD focused on management of renal osteodystrophy and secondary hyperparathyroidism. The goals of therapy were to prevent symptoms or provide symptom relief, and control the mineral abnormalities of high serum phosphorus, low serum calcium, and progressive increases in serum PTH. More recently, due to the recognition that serum calcium, phosphorus and PTH level, and vascular calcification are associated with mortality and premature cardiovascular events, treatment goals were expanded to preventing premature death and cardiovascular complications. Treatment to correct abnormal serum levels of calcium and phosphorus has demonstrated efficacy across many randomized trials, while evidence of high certainty that such treatment makes a difference to clinical outcomes including fracture, mortality and cardiovascular events has remained elusive despite a wealth of clinical research.

Phosphate Lowering

Phosphate binders reduce phosphorus absorption from dietary content through binding within the gut (Box 36.1). Given the strong association between elevated serum phosphorus that occurs in the later stages of CKD with vascular and metastatic calcification, phosphate binders have been universally adopted into routine care and were recommended in early guidelines [71], despite there being no high-quality evidence that these agents prevent symptoms or bone and cardiovascular complications of CKD.

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Box 36.1 Agents used as Phosphate Binders

Mineral salts
- Calcium carbonate
- Calcium acetate
- Calcium citrate
- Magnesium hydroxide
- Magnesium carbonate

Metal-based compounds
- Aluminum hydroxide
- Lanthanum carbonate
- Iron salts

Nonabsorbed polymers and resins
- Sevelamer hydrochloride
- Sevelamer carbonate

Aluminum

Aluminum hydroxide came into widespread use in the mid- to late 1970s, although subsequently drew concern because of case series that associated aluminum accumulation with neurotoxicity and other tissue toxicities, well-studied disease outbreaks associated with parenteral aluminum from dialysate, experimental models of aluminum toxicity, and the observation that chelation therapy appeared to modify the natural history of toxicity in cases attributed to oral aluminum exposure [72–78]. Evidence supporting the view that aluminum salts may be harmful and less effective than calcium-based binders infer that there is not a level of aluminum exposure that is safe during long-term use [78, 79].

Nonaluminum Phosphate Binders

Numerous RCTs of phosphate binders have been conducted, although most evaluate therapy for a few weeks or months and compare newer phosphate binders against calcium-containing salts [80]. Placebo-controlled trials have small sample sizes and are designed to prove the efficacy of therapy to lower serum phosphorus.

A network meta-analysis of RCTs evaluating phosphate binders, except for aluminum salts, provides evidence for comparative efficacy and safety against other phosphate binder classes or placebo or standard therapy in the absence of head-to-head trials (Table 36.3) [7]. Compared with placebo, all phosphate binder classes lower serum phosphorus, and iron-based binders lead to greater reductions than sevelamer, lanthanum, and calcium. Despite this, it is very uncertain whether phosphate binders prevent death, fracture, or need for parathyroidectomy when compared with either calcium-based binders or placebo. Sevelamer (carbonate or hydrochloride) may prevent death compared with calcium-based binders, although confidence in this evidence is low due to important methodological limitations in the available trials. It is also uncertain whether sevelamer lowers mortality, calcium biners increase mortality, both, or neither.

Sevelamer and lanthanum binder classes probably incur less hypercalcemia than calcium-based binders. The longer-term consequences of less hypercalcemia and calcium exposure with noncalcium binders is not deducible from randomized trials.

Adverse effects appear specific to specific phosphate binder classes. Sevelamer ranks as the highest probability of causing constipation, while lanthanum ranks highest for nausea and iron binders rank highest for diarrhea. Phosphate binders account for one-half of the daily pill burden for patients treated with dialysis, which is associated with lower health-related QoL [81].

Magnesium carbonate, magnesium hydroxide, and other magnesium salts bind phosphorus. In a short-term study magnesium carbonate lowered calcium ingestion from phosphate binding agents [82]. In a network meta-analysis, there was little or no high-quality evidence pertaining to patient-centered outcomes for magnesium-based binders [5].

It remains uncertain when, along the spectrum of CKD, phosphate binders should be initiated, what level of serum phosphorus should be targeted to improve outcomes, and whether all phosphate binders are equivalent in terms of long-term outcomes. There is currently no evidence based on randomized trials that specific target levels of serum phosphorus improve clinical endpoints. In a trial involving patients with CKD (stages 3b and 4) increases in coronary calcification artery calcium volume particularly among patients at caution may be needed for the use of phosphate-binding therapy for patients with normal serum phosphorus levels [83].

Dietary Modification

Clinical practice guidelines suggest lowering dietary intake of phosphorus to control serum phosphorus [10]. A Cochrane review identified there is low-quality evidence that dietary phosphorus restriction makes any difference to clinical outcomes, although dietary modification did lower serum phosphorus by 0.18 mmol/l on average [84]. In uncontrolled studies, there is no evidence of an association between phosphate intake (as estimated by 24-hour excretion) and serum phosphorus [85] or cardiovascular disease and mortality [86].

Dialysis Duration and Frequency

Frequent or longer hours dialysis lowers serum phosphorus levels. In the Frequent Hemodialysis Network (FHN)

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Table 36.3 Summary of findings: phosphate binder therapy.

Outcomes	No. of participants (no. of studies)	Absolute number of patients affected per 1000 patients treated for 1 year (95% CI)	Relative risk (95% confidence interval)	Certainty of the evidence (GRADE)	Conclusion
Sevelamer versus calcium-based binder					
All-cause mortality	6376 (20)	122 fewer (158 to 52 fewer)	0.39 (0.21 to 0.74)	Low ●○○○	Sevelamer may prevent death
Cardiovascular death	2712 (4)	100 fewer (138 fewer to 61 more)	0.33 (0.08 to 1.41)	Very low ○○○○	It is uncertain whether sevelamer makes any difference to cardiovascular mortality
Fracture	- (—)	—	No studies	Absent	No studies were found that evaluated the impact of sevelamer on fracture
Parathyroidectomy	- (—)	—	No studies	Absent	No studies were found that evaluated the impact of sevelamer on parathyroidectomy
Constipation	7862 (27)	12 more (0 to 38 more)	2.12 (1.01 –4.45)	Moderate ●●○○	Sevelamer probably leads to constipation compared with calcium-based binders
Nausea	7265 (26)	2 fewer (10 fewer to 16 more)	0.84 (0.34–2.08)	Low ●○○○	It is uncertain whether sevelamer leads to nausea
Hypercalcemia	5159 (21)	76 fewer (82–62 fewer)	0.14 (0.07 –0.29)	Moderate ●●○○	Sevelamer probably leads to less frequent hypercalcemia than calcium-based binders
Lanthanum versus calcium-based binder					
All-cause mortality	6376 (20)	Not estimable	0.78 (0.16–3.72)	Very low ○○○○	It is uncertain whether lanthanum decreases mortality
Cardiovascular death	- (—)	—	No studies	Absent	No studies were found that studied the impact of lanthanum on cardiovascular mortality
Fracture	- (—)	—	No studies	Absent	No studies were found that evaluated the impact of lanthanum on fracture
Parathyroidectomy	- (—)	—	No studies	Absent	No studies were found that evaluated the impact of lanthanum on parathyroidectomy
Constipation	7862 (27)	18 fewer (38 fewer to 18 more)	0.70 (0.37–1.30)	Low ●○○○	It is uncertain whether lanthanum leads to constipation
Nausea	7265 (26)	144 more (0 to 456 more)	2.18 (1.00–4.74)	Low ●○○○	Lanthanum may lead to nausea
Hypercalcemia	5159 (21)	109 fewer (116–90 fewer)	0.09 (0.03–0.25)	Moderate ●●○○	Lanthanum probably leads to less frequent hypercalcemia than calcium-based binders

(*Continued*)

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Table 36.3 (Continued)

Outcomes	No. of participants (no. of studies)	Absolute number of patients affected per 1000 patients treated for 1 year (95% CI)	Relative risk (95% confidence interval)	Certainty of the evidence (GRADE)	Conclusion
Iron-based binders versus calcium-based binder					
All-cause mortality	6376 (20)	Not estimable	0.37 (0.09 to 1.60)	Very low ○○○○	It is uncertain whether iron-based binders decrease mortality
Cardiovascular death	2913 (5)	Not estimable	0.50 (0.007 to 33)	Very low ○○○○	It is uncertain whether iron-based binders decrease cardiovascular mortality
Fracture	- (—)	—	No studies	Absent	No studies were found that evaluated the impact of iron-based binders on fracture
Parathyroidectomy	- (—)	—	No studies	Absent	No studies were found that evaluated the impact of iron-based binders on fracture
Constipation	7265 (26)	8 fewer (18 fewer to 15 more)	0.67 (0.28–1.61)	Low ●○○○	It is uncertain whether iron-based binders lead to constipation
Nausea	7265 (26)	Not estimable	0.53 (0.17–1.69)	Low ●○○○	It is uncertain whether iron-based binders lead to nausea
Hypercalcemia	5159 (21)	Not estimable	0.10 (0.007–1.30)	Low ●○○○	It is uncertain whether iron-based binders lead to less frequent hypercalcemia

CI: confidence interval. Data for all stages of chronic kidney disease (1–5, including 5D) are combined as there were few studies involving only people with CKD stages 1–4. Treatment estimates are drawn from a systematic review with network meta-analysis of randomized controlled trials [5]. GRADE assessment of the certainty of the evidence [9]: High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different* is low. Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different* is moderate. Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different* is high. Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different* is very high. **Substantially different = a large enough difference that it might affect decision-making.*

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Daily Trial, dialysis six times per week lowered serum phosphorus by 0.18 mmol/l compared with dialysis three times per week [87]. Similarly, frequent nocturnal hemodialysis lowered serum phosphorus levels by 0.45 mmol/l compared with conventional hemodialysis [88]. However, whether these changes in serum phosphorus translate into improved clinical outcomes is uncertain.

In summary, these data suggest phosphate binder therapy may be used to lower serum phosphorus levels in patients with CKD. Patients with CKD (any stage) may reasonably choose not to receive phosphate binder therapy based on the very low certainty that treatment makes a difference to skeletal, cardiovascular, or QoL outcomes. There is limited evidence dietary modification or higher dose dialysis to lower serum phosphorus improves clinical endpoints. The specific choice of phosphate binder may be determined by patient preferences for the avoidance of specific adverse effects together with considerations of drug availability and cost.

Lowering Serum Parathyroid Hormone and Maintaining Serum Calcium

There are five principal modalities of treatment to treat elevated serum PTH levels and maintain serum calcium levels. These include (i) vitamin D compounds and synthetic analogs, (ii) calcimimetic agents, (iii) combinations of pharmacological interventions (vitamin D plus calcimimetic), (iv) lowering dialysate calcium, and (v) surgical parathyroidectomy Box 36.2.

Vitamin D

The natural history of untreated CKD-MBD is characterized by marked skeletal disability and hypocalcemia causing tetany. Early studies demonstrated that 25-hydroxy-cholecalciferol and calcitriol increased serum calcium, suppressed PTH, and stabilized bone histology [89–93], but promptly incurred hypercalcemia, elevated renal calcium excretion, and accelerated progression of kidney failure in a dose-dependent manner [94, 95]. Lower calcitriol doses suppressed PTH with lower risks of a hypercalcemic response [96, 97]. Much of the evidence supporting vitamin D treatment derives from these proof-of-concept studies and longitudinal cohort studies demonstrating an association between vitamin D therapy and lower mortality, although this observation has been questioned on the basis that a survival advantage with treatment may reflect unmeasured confounding related to treatment selection and indication [98–101].

Box 36.2 Vitamin D Agents

Cholecalciferol (vitamin D_3)
Ergocalciferol (vitamin D_2)
Calcifediol (25-hydroxy-vitamin D_3)
24,25-dihydroxy-vitamin D_3
Calcitriol (1,25-dihydroxy-vitamin D_3)
Alfacalcidol (1-hydroxy-vitamin D_3)
Paricalcitol (19-nor-1,25-dihydroxy-vitamin D_2)
Maxacalcitol (22-oxa-calcitriol)
Doxercalciferol (1-alpha-hydroxy-vitamin D_2)
Falecalcitriol (26,27-hexfluoro-calcitriol)

In 2009, two Cochrane reviews summarized the evidence for vitamin D therapy for patients with CKD stages 1–5 not requiring dialysis [1] and those with CKD stage 5D [2] (summarized in Table 36.4), respectively. Evidence for beneficial effects of vitamin D therapy is restricted to effects on bone histology and serum PTH, as trials do not have sufficient statistical power to provide definitive evidence on clinical outcomes.

In patients with CKD stages 1–5 and stage 5D, there is very low certainty that vitamin D therapy makes any difference to mortality, commencement of dialysis, need for parathyroidectomy, bone pain, or fracture. Vitamin D therapy lowers PTH by 5.6 pmol/l for patients with CKD stages 1 to 4 and 22 pmol/l, for those with stage 5D, while incurring hypercalcemia. Two randomized trials have demonstrated oral activated vitamin D does not improve cardiac function for patients with CKD stages 3–5 during 1 year of treatment [102, 103].

Vitamin D Analogs

Vitamin D therapy is limited by hypercalcemia and hyperphosphatemia, leading to the development of structurally modified derivatives with altered affinity for vitamin D binding proteins and vitamin D receptor to ameliorate treatment-related adverse effects on calcium and phosphorus. These include paricalcitol, 22-oxacalcitriol, doxercalciferol, and falecalcitriol. Based on a systematic review of randomized trials, there is limited evidence of different effects of vitamin D analogs on hypercalcemia, hyperphosphatemia, PTH levels, or clinical outcomes including bone pain, parathyroidectomy, or mortality compared with calcitriol or other vitamin D compounds [104].

Nutritional Vitamin D

Vitamin D_3 (cholecalciferol) is synthesized in the skin from cholesterol through a chemical reaction dependent on UVB radiation derived from sunlight. Vitamin D_2 is synthesized from radiation of ergosterol, a compound derived from the mold, ergot. In a systematic review of RCTs in 2010, five trials of cholecalciferol for 6 months on average in patients with all stages of CKD were identified [105]. In low to moderate quality evidence, cholecalciferol (20 000 IU

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Table 36.4 Summary of findings: vitamin D therapy.

Outcomes	No. of participants (no. of studies)	Absolute effect per 1000 patients treated for 1 yr (95% CI)	Relative risk (95% confidence interval)	Certainty of the evidence (GRADE)	Conclusion
Chronic kidney disease stages 1–4					
All-cause mortality	477 (4)	Not estimable	1.40 (0.38–5.15)	Very low ○○○○	It is uncertain whether vitamin D prevents mortality
Fracture	76 (1)	Not estimable	Not estimable	Very low ○○○○	It is uncertain whether vitamin D prevents fracture
Parathyroidectomy	76 (1)	Not estimable	Not estimable	Very low ○○○○	It is uncertain whether vitamin D prevents parathyroidectomy
Bone pain	- (—)	Not estimable	Not estimable	Absent	No studies were found that evaluated the impact of vitamin D on bone pain
Commencing dialysis	301 (4)	Not estimable	0.76 (0.36–1.62)	Very low ○○○○	It is uncertain whether vitamin D prevents the need to commence dialysis
Hypercalcemia	712 (4)	24 more (3 to 96 more)	3.04 (1.17–7.90)	Moderate ●●○○	Vitamin D probably causes hypercalcemia
Chronic kidney disease stage 5D					
All-cause mortality	233 (5)	Not estimable	1.34 (0.34–5.24)	Very low ○○○○	It is uncertain whether vitamin D decreases mortality.
Fracture	181 (4)	Not estimable	1.00 (0.06 –15.4)	Very low ○○○○	It is uncertain whether vitamin D prevents fracture
Parathyroidectomy	133 (2)	Not estimable	0.82 (0.05–12.5)	Very low ○○○○	It is uncertain whether vitamin D prevents parathyroidectomy
Bone pain	109 (4)	Not estimable	0.29 (0.03–2.63)	Very low ○○○○	It is uncertain whether vitamin D prevents bone pain
Hypercalcemia	182 (5)	33 more (2 fewer to 180 more)	3.80 (0.90–16.1)	Low ●○○○	Vitamin D may cause hypercalcemia

CI: confidence interval. Treatment estimates are drawn from two Cochrane reviews [1, 2]. GRADE assessment of the certainty of the evidence [9]: High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different* is low. Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different* is moderate. Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different* is high. Very low; This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different* is very high. **Substantially different = a large enough difference that it might affect decision-making*.

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weekly to 25 000 IU once monthly) reduces serum PTH levels to some extent (3.5 pmol/l), without evidence of increases in serum calcium or phosphorus. Calcifediol (25-hydroxy-vitamin D_3) is converted to calcitriol by 1α-hydroxylase predominantly in the kidney, remaining under feedback regulation. In evidence from two short-term randomized trials (26 weeks or less), calcifediol lowers serum PTH levels in a dose-dependent manner for patients with hyperparathyroidism and vitamin D insufficiency [106, 107]. The effects of nutritional vitamin D supplementation for patients with CKD is unknown.

In summary, vitamin D compounds can be used to lower serum PTH levels for patients with CKD. Patients with CKD (any stage) may reasonably choose not to receive vitamin D compounds based on the very low certainty that treatment makes a difference to longer term outcomes including skeletal symptoms, bone deformities and symptoms, or cardiovascular complications and mortality.

Calcimimetic Therapy

Calcimimetic therapy mimcs the action of calcium on the calcium-sensing receptor in parathyroid tissue and suppresses PTH release. Two calcimimetic agents are approved for use in the USA by the US Food and Drug Administration (FDA) for treatment of secondary hyperparathyroidism in CKD stage 5D: oral cinacalcet and parenteral etelcalcitide. Cinacalcet is approved for marketing authorization in Europe [108]. Randomized trials have demonstrated cinacalcet lowers elevated PTH levels by 33 pmol/l on average for patients with CKD [109–111] Box 36.3.

A meta-analysis of RCTs comparing cinacalcet with placebo was published in 2013 involving 18 studies in 7446 adults with CKD (predominantly CKD Stage 5D) [112]. A summary of the findings is shown in Table 36.5. Given at 30–180 mg per day for a median of 6.5 months, there is high certainty that cinacalcet makes no difference to all-cause mortality for patients with CKD stage 5D and has uncertain effects on cardiovascular death. For patients with CKD stages 3–5, evidence for mortality was of low certainty. It is uncertain whether cinacalcet prevents fracture in CKD stage 5D and this outcome has not been evaluated in people with earlier stages of CKD. Cinacalcet leads to slightly fewer parathyroidectomy operations for people with CKD stage 5D.

Cinacalcet causes hypocalcemia for 60 patients in every 1000 treated for 1 year, and 150 more patients probably experience nausea. Additional prespecified subgroup analyses are reported from the Evaluation of Cinacalcet Hydrochloride Therapy to Lower Cardiovascular Events (EVOLVE) trial, in which cinacalcet was evaluated against placebo in nearly 4000 patients with CKD stage 5D [113]. A treatment-age interaction led to speculation that cinacalcet may be efficacious among older adults over 65 years of age, although caution is needed with this interpretation, as the EVOLVE study was not specifically designed to test this hypothesis [114]. Further trials are specifically needed among older patients to determine whether cinacalcet lowers mortality in CKD stage 5D.

Evidence for parenteral etelcalcetide in CKD is limited to a phase 2 dose-escalation trial [115], pooled data from two placebo-controlled randomized clinical trials [116], and a noninferiority trial comparing etelcalcetide with cinacalcet [117], all involving hemodialysis patients. Etelcalcetide suppresses PTH levels, while leading to some patients experiencing muscle spasm, nausea, or vomiting during 26 weeks of treatment. Etelcalcetide probably decreases serum PTH levels to a similar extent to cinacalcet. Effects of etelcalcitide on patient-level outcomes are uncertain.

The single-arm BONAFIDE study has characterized the bone response to cinacalcet therapy in 77 patients with CKD stage 5D, serum PTH >33 pmol/l, and biopsy-proven high bone turnover, after 6–12 months of cinacalcet treatment [118]. Cinacalcet may normalize bone metabolism, although two participants developed adynamic bone disease concomitant with lower PTH levels (<16.5 pmol/l) and one patient with hypophosphatemia developed osteomalacia. Similarly, Lien et al. evaluated the effects of cinacalcet on BMD over 26 weeks in 14 patients randomly assigned to conventional therapy or cinacalcet [119]. Cinacalcet may slightly increase BMD at the proximal femur. Although these two studies raise the hypothesis that cinacalcet may improve bone histology, a high-quality trial of clinical bone outcomes such as fracture, deformity, or disability is needed to provide evidence for clinical decision-making.

Box 36.3 Calcimimetic Agents

Cinacalcet
Etelcalcitide

Surgical Parathyroidectomy

Numerous case series and cohort studies have demonstrated that surgical parathyroidectomy reduces PTH levels in dialysis patients with secondary hyperparathyroidism. Prospective surgical cohorts have also described the rate of complications, the "optimal" surgical technique to increase the probability of maintaining target PTH levels postoperatively, and the effects of parathyroidectomy on the bone component of CKD-MBD, on postoperative serum calcium levels, and the need for vitamin D supplementation [120–124].

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Table 36.5 Summary of findings: calcimimetic therapy.

Outcomes	No. of participants (no. of studies)	Absolute effect per 1000 patients treated for 1 year (95% CI)	Relative effect	Certainty of the evidence (GRADE)	Conclusion
Chronic kidney disease stages 1–4					
All-cause mortality	458 (2)	18 fewer per 1000 (23 fewer to 12 more)	0.29 (0.06–1.48)	Low ●○○○	It is uncertain whether calcimimetic therapy prevents death
Parathyroidectomy	- (–)	—	No studies	Absent	No studies were found that evaluated the impact of calcimimetic therapy on parathyroidectomy
Fracture	- (–)	—	No studies	Absent	No studies were found that evaluated the impact of calcimimetic therapy on fracture
Hypocalcemia	449 (2)	310 more per 1000 (43 to 1910 more)	31.9 (5.3–193)	Very low ○○○○	It is uncertain whether calcimimetic therapy leads to hypocalcemia
Nausea	449 (2)	126 more per 1000 (29 to 295 more)	2.26 (1.29–3.95)	Low ●○○○	Calcimimetic therapy may lead to nausea
Chronic kidney disease stage 5D					
All-cause mortality	6502 (9)	6 fewer per 1000 (22 fewer to 10 more)	0.97 (0.89–1.05)	High ●●●●	Calcimimetic therapy results in little or no difference in mortality
Parathyroidectomy	4893 (5)	3 fewer per 1000 (4 fewer to 3 fewer)	0.49 (0.40–0.59)	High ●●●●	Calcimimetic therapy leads to slightly fewer parathyroidectomy operations
Fracture	3965 (2)	6 fewer per 1000 (8 fewer to 16 more)	0.59 (0.13–2.60)	Very low ○○○○	It is uncertain whether calcimimetic therapy prevents fracture
Hypocalcemia	6415 (12)	60 more per 1000 (41–85 more)	6.98 (5.10–9.53)	High ●●●●	Calcimimetic therapy leads to hypocalcemia
Nausea	6450 (12)	153 more per 1000 (68 to 272 more)	2.02 (1.45–2.81)	Moderate ●●○○	Calcimimetic therapy probably leads to nausea

CI; confidence interval. GRADE assessment of the certainty of the evidence [9]: High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different* is low. Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different* is moderate. Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different* is high. Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different* is very high. **Substantially different = a large enough difference that it might affect decision-making*.

Surgical parathyroidectomy has been advocated principally as a means of controlling severe hyperparathyroidism in CKD stage 5D who are refractory to medical management. There have been, to date, no long-term RCTs comparing parathyroidectomy to other modalities of controlling PTH in end-stage kidney disease (ESKD) patients with respect to mortality and significant morbidities, including pathologic fractures and cardiovascular events.

Parathyroidectomy has not been evaluated either with observational studies or with an RCT as a modality of treatment for secondary hyperparathyroidism in patients with CKD stages 3–5 not treated with dialysis. Surgical parathyroidectomy has not been evaluated long-term in comparison to medical approaches such as the use of calcimimetics, although the latter medical approach has displaced surgical parathyroidectomy in some areas of the world.

Dialysate Calcium

It was recognized more than four decades ago that elevations in serum calcium levels in dialysis-dependent patients reduced PTH levels. This led to adoption of higher dialysate calcium concentrations as the standard of care. In the 1970s, dialysate calcium levels increased from 2.5 mEq/l (and roughly equivalent to the normal serum calcium level) to 1.50–1.75 mmol/l to assist management of hypocalcemia, elevated serum PTH levels, and bone disease. As calcium salts replaced aluminum to bind phosphorus and maintain serum calcium, together with the introduction of vitamin D compounds, higher dialysate calcium concentrations were linked to hypercalcemia and dialysate calcium concentrations were lowered.

More recently, attention has been directed toward the risks associated with an increased exogenous calcium

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burden, principally based on low-quality observational data, including the oversuppression of parathyroid function and the development of low-turnover bone disease, as well as vascular calcification. Increasing dialysate calcium has been associated with mortality across 307 facilities and 17 236 patients in the Dialysis Outcomes and Practice Patterns Study (DOPPS) [125].

The KDIGO guideline for management of CKD-MBD suggests a dialysate calcium concentration between 1.25 and 1.50 mmol/l is used [10]. Emerging nonrandomized evidence indicates lower dialysate calcium concentrations (<1.25 mmol/l) are associated with hospitalization for heart failure, hypocalcemia, and intradialytic hypotension [126]. In addition, lower dialysate calcium is associated with lower serum calcium, increased serum phosphorus and PTH levels, and increased use of phosphate binders, vitamin D, and calcimimetics, indicating that low dialysate calcium may aggravate secondary hyperparathyroidism. Observational data also indicate that higher dialysate calcium concentrations (>1.75 mmol/l) are associated with higher mortality [127].

In a small RCT, low dialysate calcium (1.3 mmol/l) may slightly lower serum calcium levels (by 0.12 mmol/l) and increase serum PTH levels (by 16 pmol/l) and prescribing of calcimimetics and vitamin D therapies compared with high dialysate calcium (1.6 or 1.75 mmol/l). It is uncertain whether low dialysate calcium makes any difference to vascular calcification, left ventricular mass, or bone mineral density [128]. In a second randomized clinical trial in 225 patients treated with hemodialysis and with serum PTH levels ≤33 pmol/l, it was uncertain whether a dialysate calcium of 1.25 mmol/l made any difference to coronary artery calcification, bone histomorphometry, or adverse events compared with a dialysate calcium of 1.75 mmol/l [129].

Low Bone Mineral Density

Adults with CKD experience an increased risk of fractures due to altered bone strength. The incidence of hip fracture is approximately 7 per 1000 person-years among men and nearly 14 per 1000 person-years among women, representing a relative risk that is fourfold that of the general population for both sexes [58]. As in the general population, hip fracture is associated with high rates of death and hospitalization [130]. In patients with CKD, the degree of demineralization is correlated with the degree (stage) and/or duration of CKD [131, 132]. Additionally, demineralization may be accelerated in patients who have CKD caused by pathologies typically treated with steroids (e.g. glomerulonephrititis, lupus nephritis, etc.) and those characterized by chronic metabolic acidosis associated with renal tubular acidosis [133].

The presence of a fragility fracture or low BMD in a person with CKD can be due to osteoporosis or CKD-MBD (or combination). Therefore, it can be challenging to decide on the most appropriate clinical management of fractures in the presence of CKD, as treatment will depend on the underlying predominant pathology that may include osteoporosis, osteomalacia, high bone turnover, or adynamic bone disease. The likely etiology of a fragility fracture or low BMD is related with estimated GFR. For patients in an estimated GFR above 30 ml/min per 1.73 m^2, the predominant pathology, in the absence of elevated serum phosphorus or PTH levels, is likely to be osteoporosis. For patients in an estimated GFR below 30 ml/min per 1.73 m^2, other bone disorders may predominate and CKD-MBD should be excluded before a diagnosis of osteoporosis is probable.

Evidence is emerging for the effects of antiresorptive medications on BMD and fracture risk in CKD stages 3–5D, although the evidence of impact on patient-centered outcomes is very low quality. Possible treatments include bisphosphonates, receptor activator of nuclear factor-κB ligand (RANKL) inhibition (denusomab) and selective estrogen receptor modulators (SERM). Post hoc analyses of treatment effects in people with CKD enrolled in studies in the wider population and trials specifically evaluating therapy in the setting of CKD have become available.

Bisphosphonates

Bisphosphonates are used widely for the treatment and/or prevention of osteoporosis and its complications in the general population (Box 36.4).

These agents are eliminated via renal excretion [134, 135]. The efficacy of these agents in the treatment of osteoporosis in people without CKD is confirmed with high-certainty evidence within multiple trials [136]. The use of bisphosphonates in individuals with CKD is less well studied, resulting in low certainty evidence, and largely limited to prevention of BMD loss for recipients of a kidney transplant [137]. There is no evidence of high certainty that bisphosphonates modify clinical outcomes such as fracture or safety for people with CKD.

Box 36.4 Bisphosphonates (shown in ascending order of potency [potency relative to etidronate])

Etidronate [1]
- Clodronate [10]
- Pamidronate [100]
- Alendronate [500]
- Ibandronate [1000]
- Risedronate [2000]
- Zolendronate [10000]

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The effects of alendronate on BMD for women enrolled in the Fracture Intervention Trial (FIT) were examined post hoc in participants with CKD [138]. Women with an estimated GFR < 45 ml/min per 1.73 m^2 experienced increases in BMD (5.6%, 95% CI 4.8–6.5%) and may have experienced fewer fractures. There are no trials specifically designed to evaluate adverse events or risk of adynamic bone disease with bisphosphonates in CKD (any stage). In a pooled analysis of nine trials evaluating risedronate 5 mg daily to prevent or treat osteoporosis or steroid-induced bone disease, patients with CKD stages 3 and 4 were identified post hoc. Risedronate has uncertain effects on adverse events, kidney function, or rates of low bone turnover [139].

In a small RCT, patients treated with dialysis receiving etidronate (a low potency bisphosphonate) for 24 weeks experienced retardation of coronary artery calcification and lower aortic calcification compared with standard therapy [140]. In contrast, alendronate therapy for adults with CKD stages 3 and 4 has uncertain effects on aortic vascular calcification and kidney function [141].

Bisphosphonates have been reported to cause acute kidney injury, which may occur after some delay and is not always fully reversible [142, 143].

Denusomab

Denusomab is a human monoclonal antibody that binds and inhibits the actions of receptor RANKL, which is expressed by osteoblastic cells and mediates osteclastic bone resorption. Denusomab increases BMD [144] and prevents fracture [145] in older women with low bone density. Preliminary studies indicate that the pharmacokinetics of denusomab are not affected by kidney function, although in a single-dose study among 55 people with CKD stages 1–5D treatment was complicated by low serum calcium levels and sometimes required hospitalization for parenteral calcium supplementation [145].

At present, there are no prospective randomized trials designed to evaluate the benefits and harms of denusomab in people with CKD and low BMD. In a post hoc analysis of the FREEDOM trial, denosumab may prevent vertebral fractures in women with CKD stage 3, but treatment effectiveness was very uncertain among women with CKD stage 4 [146]. Although the authors concluded that adverse events were not increased, there was no information given about individual adverse events, particularly low serum calcium levels.

Raloxifene

Raloxifene is an oral SERM that increases BMDs Three trials provide information about raloxifene for women with low bone density and CKD, but evidence is limited by uncertainty of effects on in nonvertebral bone, and very low certainty about safety and fracture endpoints. In 50 women on dialysis and osteoporosis or severe osteopenia, raloxifene 60 mg daily may increase lumbar spine BMD [147]. Similarly, in a trial involving 60 women with CKD stage 5 and 5D, raloxifene treatment for 8 months may increase BMD significantly at the lumbar spine [148]. In a post hoc analysis of a multicenter randomized placebo-controlled trial, raloxifene may increase vertebral BMD, but has uncertain effects on fracture and adverse events among women with an estimated GFR below 60 ml/min per 1.73 m^2 [149]. Thus, there is no high-quality evidence that antiresorptive treatment strategies, including raloxifene, are effective or safe in people with CKD and low bone mineral density.

In summary, these data do not lead to a recommendation about treatment for low BMD for patients with CKD.

Target Levels of Serum Parathyroid Hormone, Phosphorus, and Calcium

Although specific target ranges for serum phosphorus and PTH have been previously suggested by clinical practice guidelines [71], there are no RCTs that evaluate whether these serum targets make any difference to clinical outcomes [7]. Accordingly, the KDIGO guidelines provide weak recommendations based on low-quality evidence (Box 36.5).

In summary, these data do not allow a recommendation that treatment for CKD-MBD should include specific serum targets for phosphorus or PTH.

Box 36.5 Target serum levels of parathyroid hormone, phosphorus, and calcium suggested in clinical practice guidelines

Serum biochemical parameter	CKD stage	Kidney Disease: Improving Global Outcomes (KDIGO) (2017) [10]
Phosphorus	3 and 4	Toward normal range (*2C*)
	5D	Toward normal range (*2C*)
Calcium	3 and 4	Avoid hypercalcemia (*2C*)
	5D	Avoid hypercalcemia (*2C*)
Intact parathyroid hormone	3	Optimal level is not known Patients should be assessed when levels above upper limit of normal (*2C*)
	4	Optimal level is not known Patients should be assessed when levels above upper limit of normal (*2C*)
	5D	Optimal level is not known Patients should be assessed when levels above upper limit of normal (*2C*)

Grade for strength of recommendation: level 1, strong' level 2, weak. Grade for quality of evidence: A, high, B, moderate, C, low, D, very low.

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Bone Disease After Kidney Transplantation

In a recently updated Cochrane review, 50 randomized trials have evaluated bisphosphonates, vitamin D, teriparatide (synthetic PTH), denusomab, cinacalcet, parathyroidectomy, and calcitonin [150]. Bisphosphonates are the most commonly assessed treatment approach for prevention of fracture after kidney transplantation (Table 36.6).

Evidence for treatment of bone disease after kidney transplantation is generally of low or very low certainty based on the methodological limitations in randomized trials. As the rates of fracture are low in available trials and existing trials involve small numbers of participants, existing research studies lack statistical power to provide high-quality evidence that treatment makes a difference to bone-related patient outcomes.

Table 36.6 Summary of findings: treatments for bone disease after kidney transplantation.

Outcomes	No. of participants (no. of studies)	Absolute effect (per 1000 patients treated for 1 year)	Relative effect (95% CI)	Certainty of the evidence (GRADE)	Conclusion
Bisphosphonates					
Fracture	765 (13)	38 fewer (61 fewer to 1 more)	0.62 (0.38–1.01)	Low ●○○○	Bisphosphonates may prevent bone fracture for recipients of a kidney transplant
Bone pain	153 (3)	133 fewer (160–12 fewer)	0.20 (0.04–0.93)	Low ●○○○	Bisphosphonates may prevent bone pain for recipients of a kidney transplant
Spinal deformity	- (—)	—	No studies	Absent	No studies were found that evaluated the impact of bisphosphonate therapy on spinal deformity
Graft loss	332 (6)	Not estimable	1.01 (0.42 to 2.44)	Very low ○○○○	It is very uncertain whether bisphosphonate therapy makes any difference to graft loss
All-cause mortality	606 (10)	Not estimable	0.62 (0.23 to 1.63)	Very low ○○○○	It is very uncertain whether bisphosphonate therapy makes any difference to all-cause mortality
Nausea	- (—)	—	No studies	Absent	One study was found that evaluated nausea with bisphosphonate therapy
Hypocalcemia	207 (4)	Not estimable	5.59 (1.00–31.1)	Very low ○○○○	Bisphosphonate therapy may incur hypocalcemia
Vitamin D					
Fracture	299 (5)	Not estimable	0.96 (0.10–8.94)	Very low ○○○○	It is very uncertain whether vitamin D therapy makes any difference to fracture
Bone pain	- (—)	—	No studies	Absent	No studies were found that evaluated the impact of vitamin D therapy on bone pain
Spinal deformity	- (—)	—	No studies	Absent	No studies were found that evaluated the impact of vitamin D therapy on spinal deformity
Graft loss	- (—)	—	No studies	Absent	One study was found that evaluated graft loss with vitamin D therapy
All-cause mortality	232 (3)	Not estimable	0.49 (0.03–9.22)	Very low ○○○○	It is very uncertain whether vitamin D therapy makes any difference to mortality
Nausea	- (—)	—	No studies	Absent	No studies were found that evaluated whether vitamin D therapy leads to nausea
Hypercalcemia	465 (7)	66 more (15 fewer to 300 more)	2.09 (0.84–5.22)	Very low ○○○○	It is very uncertain whether vitamin D therapy leads to hypercalcemia

CI: confidence interval. Evidence is drawn from a 2017 Cochrane review update (in peer review) [150]. GRADE assessment of the certainty of the evidence [9]: High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different* is low. Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different* is moderate. Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different* is high. Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different* is very high. **Substantially different = a large enough difference that it might affect decision-making*.

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Systematic radiological assessment for vertebral fracture is the predominant fracture-related outcome in existing randomized trials of bone therapies in kidney transplantation. Treatment in randomized trials is commenced at the time of transplantation in about half of all trials and within the first 3 years in the remaining trials. Based on 13 studies, involving 765 patients and reporting fracture events for 58 participants, bisphosphonates given for about 12 months may prevent fracture (spinal or low trauma) and bone pain. The safety profile of bisphosphonate treatment and the efficacy and safety of vitamin D for bone protection among kidney transplant recipients is very uncertain [150]. Evidence for denosumab, teriparatide, and cinacalcet is currently insufficient to inform decision-making.

In summary, these data do not allow one to recommend specific treatments for bone disease after kidney transplantation.

Patient and Caregiver Treatment Preferences

Currently, there are no studies evaluating patient and caregiver preferences for treatment or outcomes specifically in CKD-MBD. In a national workshop involving stakeholders including patients, caregivers, health providers, and researchers, lifestyle interventions and those interventions that can improve long-term transplant outcomes, prevention, and QoL were research priorities in CKD [151]. There is currently insufficient data to recommend lifestyle or exercise interventions for CKD-MBD-related outcomes [152].

Conclusion

CKD-MBD is a frequent complication for patients with moderate to severe CKD and is a central component of specialist nephrology care. In addition, bone loss occurs rapidly in the first few months after kidney transplantation.

No RCTs or large cohort studies have provided evidence of high certainty to support practices of monitoring serum biochemical markers, bone disease or vascular and non-vascular calcification. At this time, there is insufficient high-quality evidence that treatments improve patient-centered outcomes. At present, treatment for CKD-MBD can be guided by shared decision-making based on patient preferences and therapeutic safety and cost.

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37

Nutritional Disorders in Chronic Kidney Disease: Pathophysiology, Detection, and Treatment

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Introduction

Nutritional status is one of the main modifiable factors that affect the prognosis and evolution of patients with acute and chronic kidney disease (CKD) (Table 37.1). In CKD, dietary factors may have an influence on important clinical outcomes, including disease progression, quality of life, morbidity, and mortality. Due to the kidney's unique role in nutrient metabolism, patients with kidney failure are unable to maintain adequate nutrient homeostasis. As kidney disease progresses, there is a reduction in the excretion of solutes, which results in sodium and volume overload, hyperkaliemia, hyperphosphatemia, and metabolic acidosis. In addition, uremic toxins accumulation leads to reduced appetite with increased risk for suboptimal energy and nutrient intake, altered hormone regulation, and inflammation, all together exacerbating the risk for the so-called protein-energy wasting (PEW) syndrome. This syndrome is defined as a state in which there is a decrease in protein and energy stores, usually associated with a lower functional ability to adapt to stress situations and worse patient survival [18–22].

Many factors contribute to the nutritional status of the CKD patient, such that there is no definitive marker to diagnose PEW nor a single treatment to reverse this state. In the CKD patient, PEW can be produced both by undernutrition and by other factors unrelated to nutrient intake, such as the appearance of intercurrent catabolic processes, the loss of nutrients through urine or dialysate, metabolic acidosis, and endocrine alterations (e.g. growth hormone [GH] and insulin-like growth factor 1 [IGF-1] deficiencies, hyperinsulinism, hyperparathyroidism) [23–37].

Nutritional interventions should be a cornerstone strategy in the management of CKD patients, both as a renoprotective antiproteinuric measure in the predialysis stage, and to prevent overweight and malnutrition in all stages of CKD, the latter especially in later stages. Given the number of factors involved in the nutritional and metabolic status of the CKD patient, adequate dietary management will require a combination of therapeutic measures that minimize energy-protein depletion and favor the anabolic stimulus. Many of these measures, such as the correction of acidosis and the modification of renal replacement therapy, go beyond simple caloric or dietary support [38, 39].

The optimal approach to nutrition is not well known, and randomized controlled trials (RCTs) are lacking and have yielded conflicting results. This chapter examines the evidence for management of nutrition in adults with CKD stages 3–5, including dialysis and transplant patients, focusing mainly on CKD progression and PEW treatment. Evidence for nutritional interventions for CKD mineral and bone disorders (CKD-MBD), and for children with kidney failure is discussed in Chapters 36 and 38, respectively.

Nutritional Requirements for Patients with Kidney Disease

Because a "kidney diet" can have many restrictions, adherence to such a diet can be difficult and troublesome. In addition, the optimal diet for CKD patients varies depending

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Table 37.1 Nutritional interventions for CKD.

Treatment	Recommendation	Certainty of evidence	Strength of recommendation
Dietary interventions, including dietary patterns and nutritional counseling	We suggest dietary interventions can be used to improve health-related quality of life, blood pressure control, eGFR, and nutritional status assessed by albumin levels. Patients with CKD (any stage) may reasonably choose not to receive dietary interventions based on the very low certainty that treatment makes a difference to longer term outcomes including survival, cardiovascular morbidity, and development of ESRD.	High (blood pressure control) Moderate (serum albumin levels) Low (health-related quality of life, eGFR) Very low (mortality, cardiovascular events, progression to ESRD)	Weak [1]
Dietary protein restriction, including LPD and VLPD	We suggest dietary protein restriction can be used to reduce the risk for development of ESRD in both nondiabetic and diabetic patients with CKD stages 3–5, and to reduce both mortality and risk for development of ESRD in type 1 diabetic patients with ND-CKD. Patients with CKD may reasonably choose not to receive dietary protein restriction as treatment makes no difference to mortality or PEW development.	High (mortality) Moderate (development of ESRD) Very low (development of PEW)	Weak [2–5]
Dietary salt restriction	We suggest dietary salt restriction can be used to reduce blood pressure, antihypertensive medication dosage, proteinuria, and edema for patients with CKD. Patients with CKD may reasonably choose not to receive dietary salt restriction based on the very low certainty that treatment makes a difference to longer term outcomes including health-related quality of life, survival, cardiovascular morbidity, and the development of ESRD.	High (blood pressure, proteinuria) Very low (mortality, cardiovascular morbidity, development of ESRD)	Weak [6, 7]
Dietary caloric restriction to reduce weight	We suggest dietary caloric restriction can be used to reduce proteinuria and blood pressure, as well as hyperfiltration in ND-CKD patients. Patients with CKD may reasonably choose not to receive dietary caloric restriction based on the very low certainty that treatment makes a difference to the development of ESRD.	Moderate (blood pressure, proteinuria) Very low (development of ESRD)	Weak [8]
Probiotics supplementation	We suggest probiotics supplementation may be used to reduce p-cresyl sulfate levels. Patients with CKD may reasonably choose not to receive probiotics supplementation based on the very low certainty that treatment makes a difference to longer term outcomes including health-related quality of life, survival, cardiovascular morbidity, and the development of ESRD.	Very low	Weak [9]
Oral nutritional supplements	We suggest oral nutritional supplements may be used to improve nutritional status by increasing serum albumin levels and body mass index in dialysis patients, without influence on serum potassium and phosphorus levels. Patients with CKD (any stage) may reasonably choose not to receive probiotics supplementation based on the very low certainty that treatment makes a difference to survival.	Very low	Weak [10]
Intradialytic parenteral nutrition	We suggest intradialytic parenteral nutrition may be tested to improve nutritional status in hemodialysis patients with PEW if nutrient requirements can be achieved in combination with oral intake. Hemodialysis patients with PEW may reasonably choose not to receive intradialytic parenteral nutrition based on the very low certainty that treatment makes a difference to longer term outcomes including survival and morbidity.	Very low	Weak [11]

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Megestrol acetate	We suggest megestrol acetate may be tested in dialysis patients to reverse poor appetite and improve nutritional status if other treatment options are unavailable and for less than 24 weeks. Dialysis patients with poor appetite may reasonably choose not to receive megestrol acetate based on safety concerns and the very low certainty that treatment makes a difference to longer term outcomes including health-related quality of life, survival, and morbidity.	Very low	Weak [12]
Fish oil supplements	We suggest fish oil supplements may be used in dialysis patients to alleviate chronic inflammation status, depression symptoms, and hypertriglyceridemia, and reduce cardiovascular events and the risk of arterio-venous-graft events. Dialysis patients may reasonably choose not to receive fish oil supplements based on the very low certainty that treatment makes a difference to longer term outcomes including health-related quality of life and survival.	High (hypertriglyceridemia) Moderate (C-reactive protein levels) Low (depression symptoms, cardiovascular events, arterio-venous-graft events) Very low (health-related quality of life, mortality, ND-CKD)	Weak [13]
L-Carnitine supplementation	We suggest L-carnitine supplements may be tested in dialysis patients to alleviate chronic inflammation status. Dialysis patients may reasonably choose not to receive L-carnitine supplements based on the very low certainty that treatment makes a difference to longer term outcomes including health-related quality of life, survival, and comorbidity.	Very low	Weak [14, 15]
Statins	We suggest statins may be used in dialysis patients to alleviate chronic inflammation status and reduce cholesterol levels. Dialysis patients may reasonably choose not to receive statins based on the moderate to very low certainty that treatment makes a difference to longer term outcomes including health-related quality of life, survival, and cardiovascular events.	High (C-reactive protein levels, cholesterol levels) Moderate (survival and cardiovascular events) Very low (health-related quality of life, ND-CKD)	Weak [16]

CKD, chronic kidney disease; LPD, low protein diet; VLPD, very low protein diet; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; ND-CKD, nondialysis chronic kidney disease.

GRADE assessment of the certainty of the evidence [17]: High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different* is low. Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different* is moderate. Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different* is high. Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different* is very high. *Substantially different = a large enough difference that it might affect decision-making.

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upon their nutritional needs, the CKD stage, the type of renal replacement therapy, and the presence of other comorbidities such as PEW, obesity, hypertension, proteinuria, or heart failure. Patient preferences, their cultural eating habits, and their economic status are additional factors to be kept in mind for improving their compliance with dietary recommendations, which should be monitored regularly.

Need for Individualization

Too many restrictions should be avoided as they may result in a reduced nutrient intake. Dietary modifications are seldom required for patients with estimated glomerular filtration rate (eGFR) ≥60 ml/min/1.73 m^2. Such patients should be advised to implement the same dietary recommendations as for the general population, consisting of low sodium and refined sugar, avoidance of red and processed meats, and high content of fruits, vegetables, legumes, fish, poultry, and whole grains. In later stages of CKD, however, the diet needs to be modified (Figure 37.1) [40]. Historically, research and guideline recommendations have been focused mainly on modifying single micro- or macronutrients intake, such as protein, sodium, potassium, or phosphate. Providing specific nutrients may prevent and treat PEW, whereas limiting the intake of certain nutrients may prevent obesity, hypertension, and proteinuria, reducing the risk of cardiovascular disease and CKD progression as well as ameliorating uremic symptoms [41]. However, the nutrient content of each type of diet tends to be steady and constant, and individual dietary habits usually remain unchanged over time, therefore the overall dietary pattern may be more decisive for patient outcomes than an excess or deficiency of specific nutrients [42].

Overall Recommendations

The current Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines recommend a protein intake ranging from 0.6 to 1.2 g/kg body weight per day according to CKD stage, of which more than half should be of high biological value. The recommended energy intake is 35 kcal/kg body weight per day for those who are younger than 60 years of age, and 30–35 kcal/kg/day for individuals who are 60 years or older [43]. These guidelines do not refer to the recommended intake of carbohydrates, lipids, or most micronutrients, with the exception of recommendations for calcium and phosphorus intake. The European guidelines give recommendations regarding the intake of vitamins, minerals, and trace elements, although they recognize that in the absence of RCTs such recommendations cannot be considered true clinical guidelines, but rather reflect only the opinion of experts [44]. Overall, many of the nutritional requirements indicated for the CKD population are simple extrapolations based on the recommendations made for the general population, with the added classic limitations

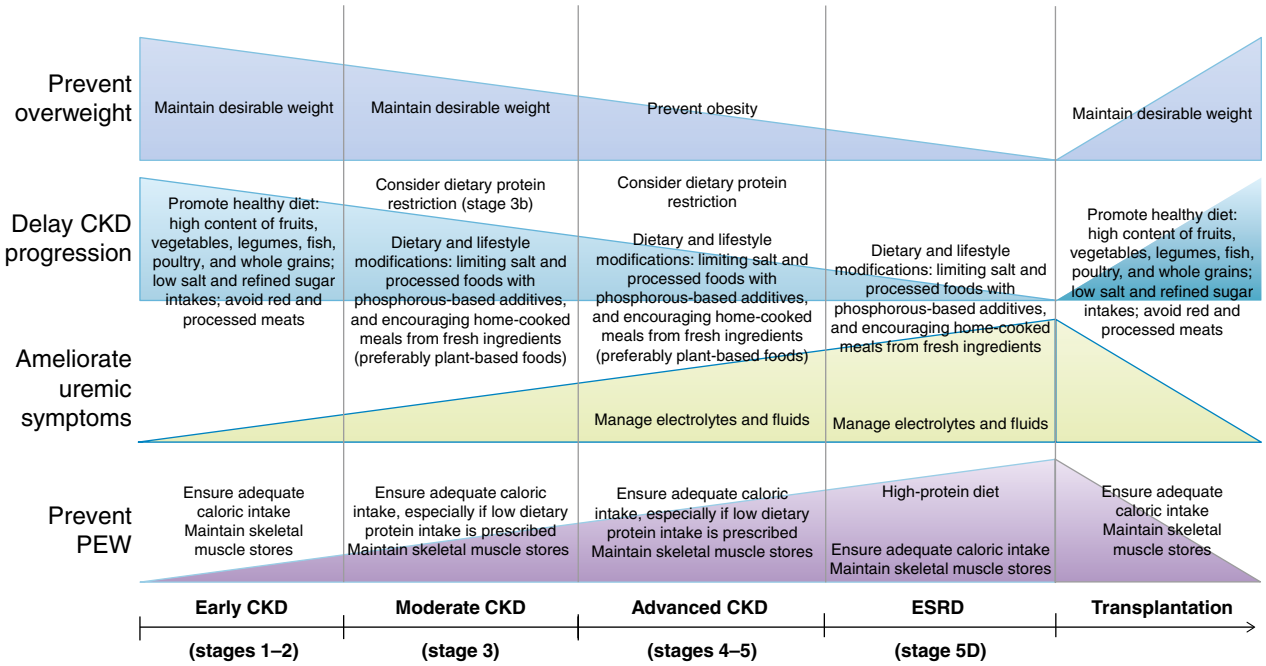

Figure 37.1 Schematic representation of the relative importance of each of the main nutritional goals across the CKD stages, including preventing overweight, delaying the development of ESRD, decreasing uremic symptoms, and preventing PEW. CKD, chronic kidney disease; PEW, protein-energy wasting.

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in potassium intake, sodium, and phosphorus, which have prevailed for more than 40 years in patients on dialysis.

However, many of these classic recommendations, which include restricting the intake of fruits, vegetables, or dairy products, are probably not adequate for current patient characteristics (i.e. old and fragile) and treatments, which range from conservative management to more intensive dialysis regimens, including nocturnal or short-daily hemodialysis (HD) [45]. Conversely, what has recently been proposed is an increase in the intake of fiber, antioxidants, and phytochemicals, which could have a very positive impact on the nutritional and cardiovascular status of CKD patients [46, 47]. In this sense, recommendations should not only be based on the quantity but also on the quality of each food, so that the choice, for example, of unprocessed foods may allow us to abandon unnecessary restrictions that can affect the quality of life of patients [45].

In addition, stable patients with precise dietary indications, both those with CKD and those on dialysis or transplanted, can develop an intercurrent acute process that requires substantially increasing their energy and protein requirements.

Table 37.2 shows the nutritional requirements for adult patients with nondialysis CKD (ND-CKD), HD, peritoneal dialysis (PD), and transplant, according to the main clinical guidelines and consensus papers [43, 44, 48–55].

Energy Requirements

Adequate caloric intake – by avoiding processed carbohydrates and saturated fat intake, and by increasing complex carbohydrates and mono- and polyunsaturated fats – must be maintained to avoid malnutrition, and conversely to prevent overweight and obesity, given their contribution to the cardiovascular risk and kidney disease progression. Due to the increased resting energy expenditure (REE) secondary to inflammation and comorbidities linked to CKD, as well as for preserving a neutral or positive nitrogen balance, current guidelines recommend a caloric intake of 30–35 kcal/kg/day, which is higher than for the general population. However, this general recommendation should be individualized according to the patient's profile, including age, lean body mass (which is the primary determinant of energy expenditure), physical activity, and the type of kidney disease [56–58].

- In ND-CKD patients under a low protein diet (LPD), an energy intake of 35 kcal/kg/day may be recommended to ensure a neutral nitrogen balance. By contrast, in sedentary, elderly, and obese patients the energy contribution should provide around 30 kcal/kg/day.
- In PD patients, about 300 kcal may be provided in each glucose-based exchange, contributing up to 30% of the total daily energy intake [59]. This additional source of calories should be taken into consideration when assessing energy intake in this population.
- In kidney transplant patients, the caloric intake should be adapted to individual needs according to physical activity and presence of low weight or obesity.
- Any intercurrent catabolic episode may require increasing energy (and protein intake) independently of CKD stage or renal replacement therapy (Table 37.2).

Protein Requirements and Source of Protein Intake

For ND-CKD stable patients, the recommended protein intake is 0.6–0.8 g/kg/day, of which at least half should be of high biological value [43, 48]. This restriction is generally well tolerated, limiting waste-product accumulation while simultaneously preserving nutrition. Benefits of lower protein diets include slowing CKD progression and reducing uremic symptoms [56, 58, 60]. Reduced protein intake is also associated with favorable laboratory and metabolic effects, including reduction of uremic toxins and acid load, with better control of hyperkalemia and hyperphosphatemia [61, 62]. Figure 37.2 summarizes the potential benefits of dietary protein restriction.

Nevertheless, the optimal degree of protein restriction remains unclear, and there is no consensus on the recommended level of protein restriction according to the degree of kidney dysfunction. There are basically two alternatives: the so-called low protein diet (LPD, 0.6–0.8 g/kg/day) and the very low protein diet (VLPD, 0.3–0.4 g/kg/day) supplemented with 7–15 g/day of ketoanalogs and essential amino acids. In both cases, patients should be carefully monitored for adequate caloric intake (30–35 kcal/kg/day) that allows a positive nitrogen balance and so that proteins are not used as a caloric source. [41, 62] The 2012 Kidney Disease, Improving Global Outcomes (KDIGO) guidelines for the management of CKD recommended lowering dietary protein intake to 0.8 g/kg/day in CKD stage 4–5 subjects with diabetes (grade 2C recommendation) and without diabetes (grade 2B recommendation), and avoiding a high protein intake (>1.3 g/kg/day) in adults with CKD at risk of progression (recommendation grade 2C). It considers the restriction of 0.6 g/kg/day nutritionally adequate given that it facilitates better control of uremic complications [63, 64].

There is no consensus on whether the source of proteins differently impacts on CKD progression risk. Although recent observational studies have suggested that plant proteins may have more reno-protective effects than animal proteins [41], confounding factors inherent to a diet rich in protein from plant sources (i.e. a higher intake of vitamins and antioxidants) make it difficult to draw conclusions [42].

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Table 37.2 Summary of nutritional requirements for patients with kidney failure.

	Early CKD (stages1–2)	CKD stages 3–5	Hemodialysis	Peritoneal dialysis	Transplantation
Energy (kcal/kg/day)[a]	30–35	30–35	30–35	30–35 (including kcal from dialysate)	30–35
Protein (g/kg/day)[b]	0.8 1.0 if intercurrent catabolic episode 0.8 (+1 g/day of high biological value protein for each g/day of urinary protein loss) if nephrotic syndrome	0.6–0.8 0.3–0.4 in selective patients with CKD 5 and conservative treatment Keto/amino acid supplementation may be considered together with dietitian support 1.0 if intercurrent catabolic episode	≥1.2 if IHD ≥1.5 if intercurrent catabolic episode 1.7 if CRRT	≥1.2 ≥1.5 if peritonitis	0.8 ≥1.4 for the first 4 weeks after transplantation or if high dose of prednisone is required 0.6–0.8 if CKD stages 3–5T
Fiber (g/day)	25–38	25–38	25–38	25–38	25–38
Sodium (mg/day)	<2.0–2.4	<2.0–2.4	<2.0–2.4	<2–2.4	<2–2.4
Potassium (mEq/day)[c]	No potassium restriction	51–102 Potassium restriction should be prescribed based on serum potassium levels	40–70 If long interdialytic interval restriction must be mandatory	Does not usually need restriction Patients with hypokalemia should increase their potassium intake	Potassium restriction should be prescribed based on the serum potassium levels
Vitamin D (IU/day)	600–800	600–800	600–800	600–800	600–800
Calcium (g/day)	≤800–1000	≤800–1000	≤800–1000	≤800–1000	≤800–1000
Phosphorus (mg/day)[d]	800–1000	800–1000	<800	<800	800–1300
Magnesium (mg/day)	200–300	200–300	200–300	200–300	200–300
Iron (mg/day)[e]	10–18	10–18	10–18	10–18	10–18
Zinc (mg/day)[f]	15	15	15	15	15

CKD, chronic kidney disease; IHD, intermittent hemodialysis; CRRT, continuous renal replacement therapy; T, transplant.

[a] Carbohydrates, which provide 40–60% of the daily energy intake, should be natural (nonrefined) and complex with a high-fiber content; 35 kcal/kg ideal body weight/day for those who are less than 60 years of age and 30–35 kcal/kg ideal body weight/day for individuals 60 years or older and sedentary people.

[b] At least 50% of dietary protein should be of high biological value.

[c] First avoid high-potassium foods with poor nutritional value and correct other causes of hyperkaliemia such as metabolic acidosis or renin-angiotensin-aldosterone system inhibitors before restricting healthy foods.

[d] Limiting processed foods with phosphorous-based additives and encouraging home-cooked meals from fresh ingredients (preferably plant-based foods) should be the first-line interventions for phosphorus restriction; the next-line strategy may be to exclude that dietary protein intake is higher than recommended, and limiting foods with high phosphorus to protein ratios.

[e] 10 mg/day for males and nonmenstruating females; supplementary iron should be given to all hemodialysis patients treated with an erythropoiesis-stimulating agent (ESA) to maintain adequate serum transferrin and serum ferritin levels, aimed to achieve a target hemoglobin (Hb), except for those receiving the iron intravenously.

[f] Zinc supplementation of 50 mg zinc element per day for 3–6 months should be considered in hemodialysis patients with a chronic inadequate protein/energy intake and symptoms evoking zinc deficiency (impaired taste or smell, skin fragility, impotence, peripheral neuropathy).

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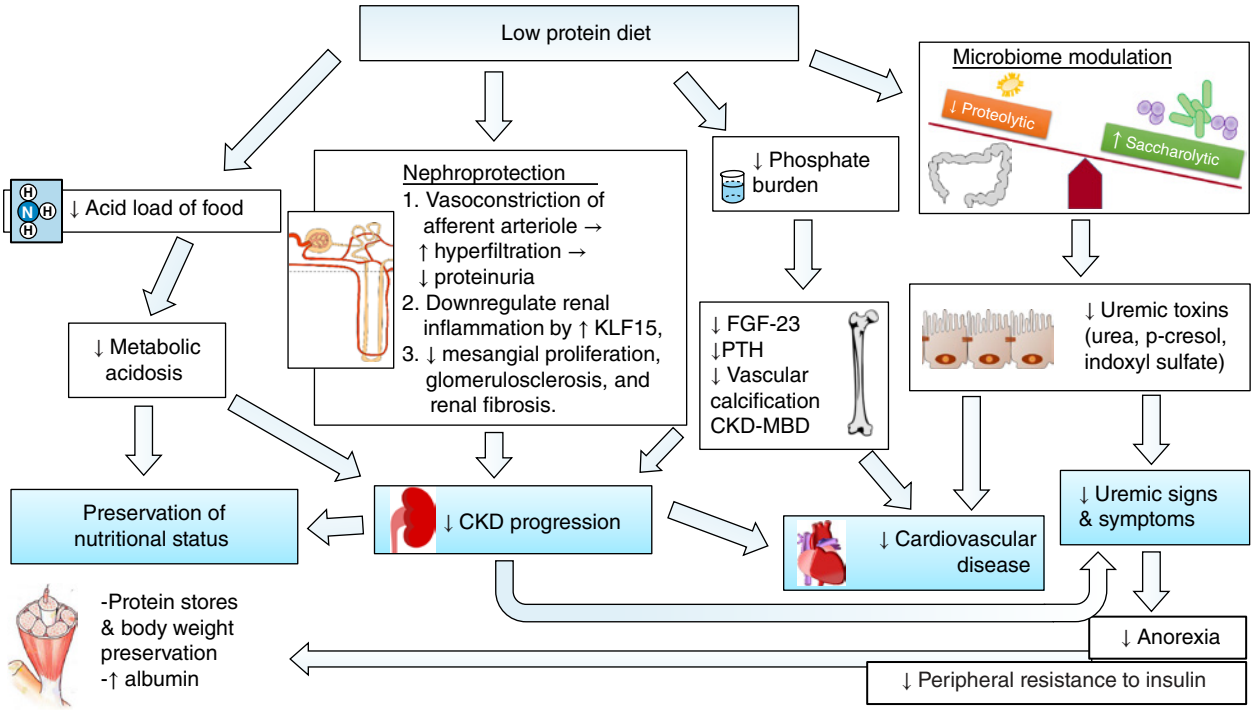

Figure 37.2 Potential benefits of low protein diet. CKD, chronic kidney disease; CKD-MBD, chronic kidney disease-mineral and bone disorder; KLF15, Kruppel-like factor-15; FGF-23, fibroblast growth factor-23; PTH, parathyroid hormone. *Source:* Adapted from: Wang et al. [60] and Chan et al. [58].

Patients transitioning to dialysis therapy with incremental dialysis, and especially those on prevalent dialysis, should increase their protein intake to 1.2–1.4 g/kg/day to prevent PEW [60]. Protein losses into the dialysate, increased energy expenditure, and inflammation related to the dialysis procedure are the main reasons for this higher protein requirement [20, 59]. Patients in any CKD stage with existing or imminent PEW due to intercurrent catabolic episodes may require an increase in protein intake (Table 37.2). For kidney transplant recipients, during the first 4 weeks after transplantation and whenever high doses of steroids are used, a protein intake of at least 1.4 g/kg/day is recommended. Due to the lack of available studies in this group of patients, it has been suggested those with normal kidney function should follow similar recommendations to the general population. In transplant patients with chronic graft dysfunction, it is recommended to provide the same protein restriction diet as in patients with ND-CKD [54].

Sodium Intake and Fluid Balance

A modest sodium restriction (<2.0–2.4 g/day of Na ≈ <5–6 g/day of NaCl) is recommended for the management of CKD patients [44, 62]. The benefits of salt restriction may include lower blood pressure (BP) and proteinuria, improved cardiovascular outcomes, and slower CKD progression [62]. For dialysis patients, it may help to decrease thirst, avoiding an excessive interdialytic weight gain and fluid overload, which are closely related to cardiovascular events and survival [65, 66].

Potassium Intake Recommendations

Most CKD patients do not require aggressive dietary potassium restriction until advanced stages. K/DOQI guidelines recommend no potassium restriction for patients with CKD stages 1–2, while a limited intake from 2 to 4 g/day (51–102 mEq/day) is recommended for patients with CKD stages 3–4 [43]. However, given that potassium is associated in the general population with lower systolic BP, lower risk of stroke, and better bone mineral density, dietary potassium restriction should be prescribed based on serum potassium levels [67–69]. Moreover, it has been suggested that high potassium foods with poor nutritional value (i.e. bran products, chocolate, or salt substitutes) should be voided and other causes of hyperkaliemia, such as metabolic acidosis or renin-angiotensin-aldosterone system inhibitors, corrected before restricting healthy foods such as fruits and vegetables [64]. For ND-CKD patients with chronic hyperkalemia, obtaining a 24-hour urine for potassium may help to determine whether decreased kidney excretion or excessive potassium intake is the cause of

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hyperkalemia. If the urine potassium content is much higher than 50 mEq/24 h, reducing potassium intake should be effective for controlling high potassium levels.

For HD patients, the long interdialytic interval may be a particularly critical period for severe hyperkalemia appearance, and potassium intake restriction may be mandatory, given the association of hyperkalemia with arrhythmia and higher mortality in this population [70].

Calcium, Phosphorus, and Vitamin D Intake Recommendations

Although K/DOQI guidelines suggest limiting total calcium intake to 1500 mg/day, including medication sources [43], there have been concerns about the safety of this recommendation, which may lead to a marked positive calcium balance and the potential development of cardiovascular calcifications [71]. Several experts recommend limiting total calcium intake to 800–1000 mg/day or less [64].

Given the role of serum phosphate in the pathogenesis of vascular calcification and the link between phosphate levels and survival in both the general and CKD populations, clinical practice guidelines suggest limiting dietary phosphate intake in the treatment of hyperphosphatemia (grade 2D recommendation) [72], with a maximum dietary phosphate intake of 800–1000 mg/day [43, 44]. Limiting processed foods with phosphorous-based additives and encouraging home-cooked meals from fresh ingredients (preferably plant-based foods) should be the first-line interventions for phosphorus restriction [64]. The next-line strategy may be to exclude excessive dietary protein intake, as well as limiting foods with high phosphorus to protein ratios [41].

The optimal dietary vitamin D intake and the optimal levels of 25-hydroxyvitamin D for CKD patients remain controversial [72, 73]. Based on the recommendations made for the general population, vitamin D intake for CKD patients is recommended at 600–800 IU/day [44, 64]. Although some interventional studies have showed some benefits of vitamin D supplementations in proteinuria and nutritional status in CKD patients, no definite conclusions can be drawn yet from this emerging evidence [74, 75]. Moreover, to date no clear benefit on skeletal outcomes can be concluded from the vitamin D administration in CKD populations [73, 75].

Fiber Intake Recommendations

Although the recommended dietary fiber intake for CKD patients is not even discussed in current nutritional guidelines, recent data suggest that fiber intake seems to provide similar [76–78], if no greater [79], benefits to those demonstrated in the general population, including improved survival, lower systemic inflammation, and less rapid CKD progression. A daily fiber intake of 25–30 g/day or more for CKD patients may be suggested, as this amount is similar to the recommendation for the general population [62]. Because of potassium restriction in advanced CKD, fruits and vegetables intake tends to be low, and dietary fiber intake is often very low [80]. Plant-based foods, with special attention to fruits and vegetables that are low in potassium, are an important source of dietary fiber that should be recommended in moderation to CKD patients, as long as the potassium levels allow [62].

Definition of Protein-energy Wasting

In the uremic milieu, a state of hypercatabolism, inflammation, and undernutrition leads to the development of PEW syndrome. This syndrome represents a maladaptive metabolic state characterized by a decrease in both protein deposits and energy reserves that appears in patients with acute or chronic kidney failure as part of a mechanism of defense of the body in response to a stress situation. PEW is a consequence of various factors that usually appear as kidney function decreases, including a spontaneous decrease in nutrient intake and various metabolic and hormonal alterations that lead to a depletion of proteins (especially skeletal muscle), and that does not recover only with diet. Table 37.3 shows the diagnostic categories defined by the International Society of Renal Nutrition and Metabolism for diagnosing PEW, including biochemical criteria, low body mass, reduced muscle mass, and low protein or energy intakes [20]. One diagnostic criterion needs to be met in at least three of the four categories for the diagnosis of PEW, so no single marker can diagnose the syndrome.

Epidemiology of Protein-energy Wasting

PEW is a common phenomenon across the spectrum of acute kidney injury (AKI) and CKD; prevalence increases in patients on dialysis and the longer they remain on dialysis [81]. However, the exact evaluation of the prevalence of PEW in the kidney population has been historically hampered by several factors, including the lack of a standardized definition for malnutrition, the variability of existing evaluation tools, the limited sample sizes of most of the studies, and the different prevalence of malnutrition in the general population reflecting economic and social disparities between different geographical regions [82]. In a recent meta-analysis from contemporary studies (2000–2014) including more than 50 subjects with kidney disease, the prevalence of PEW by Subjective Global Assessment (SGA) or Malnutrition-Inflammation Score (MIS) was estimated to range from 60% to 82%, 11% to 54%, 28% to 54%, and 28% to 54% for AKI, CKD stages 3–5, dialysis, and transplant

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Table 37.3 The ISRNM criteria for diagnosing PEW.

Criteria		Comments
Serum chemistry		
	Serum albumin <3.8 g/dl	Nonspecific. It may be influenced by fluid status, inflammation, proteinuria, dialysis procedure, intercurrent illnesses, liver disease, etc.
	Serum prealbumin (transthyretin) <30 g/dl	Only appropriate for maintenance dialysis patients (levels may vary according to GFR level for patients with nondialysis CKD).
	Serum cholesterol <100 mg/dl	It may be influenced by lipid-lowering medication.
Body mass		
	BMI <23 kg/m^2	Weight is influenced by fluid overload and does not distinguish fat from muscle.
	Unintentional nonedematous 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 of 5% over 3 months or 10% over 6 months	
	Reduced mid-arm muscle circumference area (reduction >10% in relation to 50th percentile of reference population)	Measurement must be performed by a trained anthropometrist.
	Creatinine appearance	May be influenced by both muscle mass and meat intake.
Dietary intake		
	Unintentional low DPI <0.8 g/kg/day for at least 2 months for dialysis patients or <0.6 g/kg/day for patients with CKD stages 2–5	Can be assessed by dietary diaries and interviews, or by calculation of nPCR or nPNA.
	Unintentional low DEI <25 kcal/kg/day for at least 2 months	Can be assessed by dietary diaries and interviews.

BMI, body mass index; CKD, chronic kidney disease; DEI, dietary energy intake; DPI, dietary protein intake; GFR, glomerular filtration rate; ISRNM, International Society of Renal Nutrition and Metabolism; nPCR, normalized protein catabolic rate; nPNA, normalized protein nitrogen appearance.
Note: At least one measure from at least three of the criteria should be met in order to classify a patient as having PEW. *Source:* 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: 391–398.

patients, respectively (Figure 37.3) [83]. Another recent study using the four PEW diagnostic criteria showed a prevalence of more than 50% of moderate or severe PEW in the HD population [84].

Pathophysiology

Nutritional Disorders in CKD

The kidney functions in maintaining nutrient homeostasis and the nutritional disorders that appear in CKD are depicted in Figure 37.4. During the course of CKD, the kidneys progressively lose their ability to maintain nutrient homeostasis, with a resulting reduction in the excretion of solutes and subsequent accumulation of toxic products (including protein waste products, phosphate, sodium) and water. This leads to acidemia, hyper-azotemia, hyperphosphatemia, and fluid retention. The kidneys attempt to compensate for damage through hyperfunction (hyperfiltration) of the remaining functional nephrons, and activation of several compensative mechanisms, such as secondary hyperparathyroidism (SHPT) or volume expansion, which may be harmful for the body. As a result of all these changes, several nutrient disorders arise as kidney function declines, including metabolic acidosis, systemic inflammation, and hormonal dysregulation that have been attributed to the development of hypercatabolism and risk for negative nitrogen balance [85].

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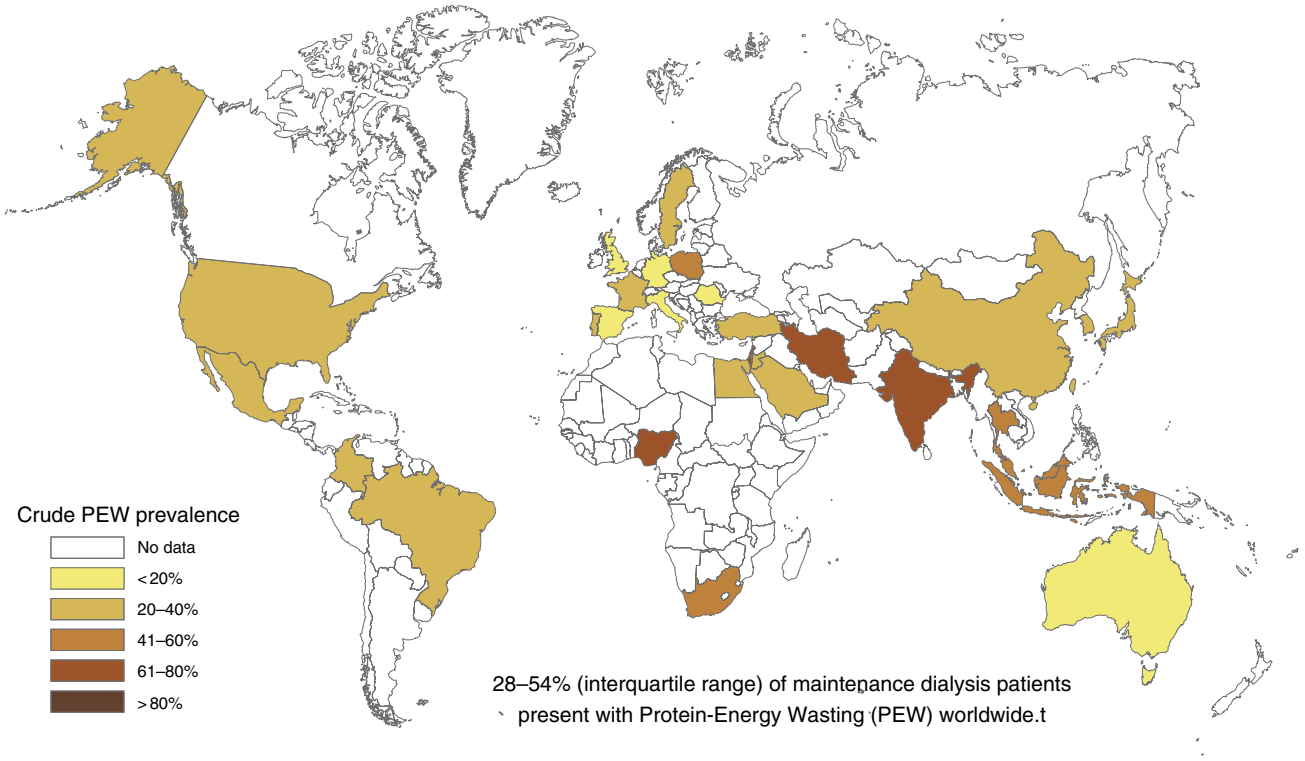

Figure 37.3 Prevalence of PEW among patients undergoing maintenance dialysis worldwide reported from studies published between 2000 and 2014. Color gradation reflects PEW prevalence in all included studies from each country (weighted averages within countries). PEW, protein-energy wasting. *Source:* From: Carrero et al. [83].

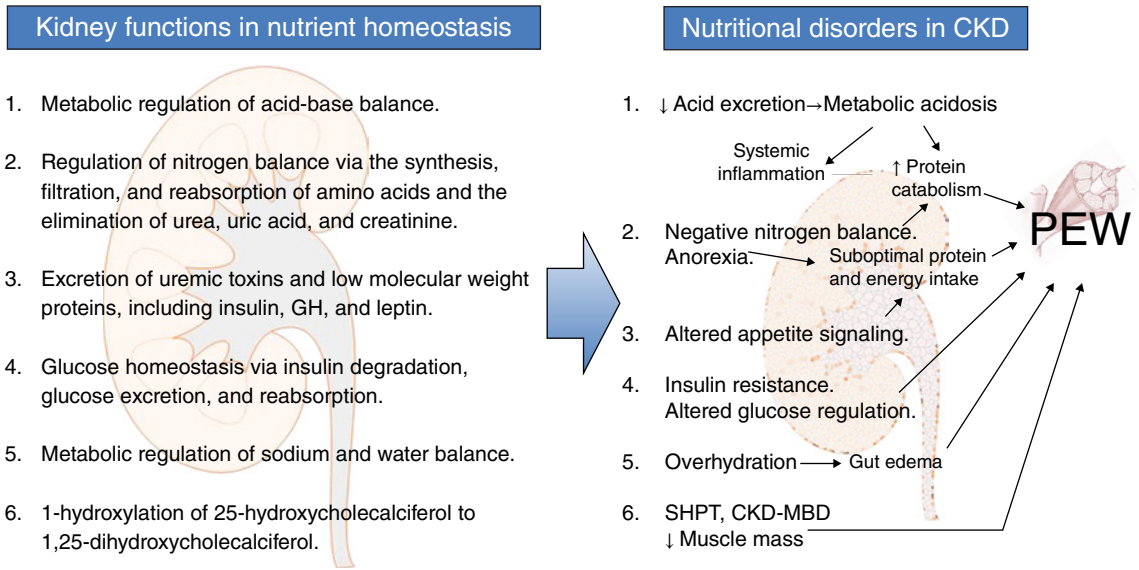

Figure 37.4 Role of the kidney in maintaining nutrient homeostasis and nutritional disorders in CKD. CKD, chronic kidney disease; CKD-MBD, chronic kidney disease-mineral and bone disorder; GH, growth hormone; PEW, protein-energy wasting, SHPT, secondary hyperparathyroidism.

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Causes of Protein-energy Wasting

Several factors contribute to the deterioration of nutritional status in CKD patients. PEW can occur due to inadequate nutrient intake, as well as other factors not related to diet, such as comorbidities, appearance of intercurrent catabolic processes, metabolic acidosis, and several endocrine disorders associated with CKD, such as deficit of GH and IGF-1, hyperinsulinism, SHPT, or hyperglucagonemia (Figure 37.5) [37]. Although clearance of uremic toxins by dialysis is able to partially reverse anorexia related to uremic syndrome, the dialysis technique itself can contribute to PEW due both to the forced loss of nutrients by the dialysate and to direct catabolic and inflammatory effects [27]. The consequences of PEW are reduction of muscle mass, increased risk of infection, and cardiovascular disease, which results in lower quality of life and survival of CKD patients [37].

Decreased Protein and Energy Intake

Uremic syndrome is associated with loss of appetite and various gastrointestinal disorders that lead to a decrease in nutrient intake. The progressive accumulation of uremic toxins, enteric hormones, adipokines (leptin, visfatin), and inflammatory cytokines that appear as kidney disease progresses are the main factors that have been related to decreased appetite [86, 87]. Underdialysis is an additional factor that contributes to anorexia and dysgeusia, so adequate dialysis is essential to preserve the nutritional status of HD patients. Several RCTs have shown that an increase in the dose of diffusive or convective dialysis allows an increase in nutrient intake. In a randomized study, an increase in the dialysis dose from Kt/V 0.8 to 1.3 increased the protein intake (estimated by the rate of normalized protein catabolic rate [nPCR]) at 3 months, whereas the control group did not show changes in Kt/V and nPCR [88]. In another trial comparing high-flux HD with on-line hemodiafiltration, the administration of a convective volume of 23.6 l allowed an increase in protein intake with a tendency to increase appetite [89]. Similar results have been observed with other more intensive dialysis regimens, such as short-daily dialysis or long nocturnal dialysis [90, 91].

The usual dietary restrictions in CKD patients, the recommendations for cooking foods to reduce the content of

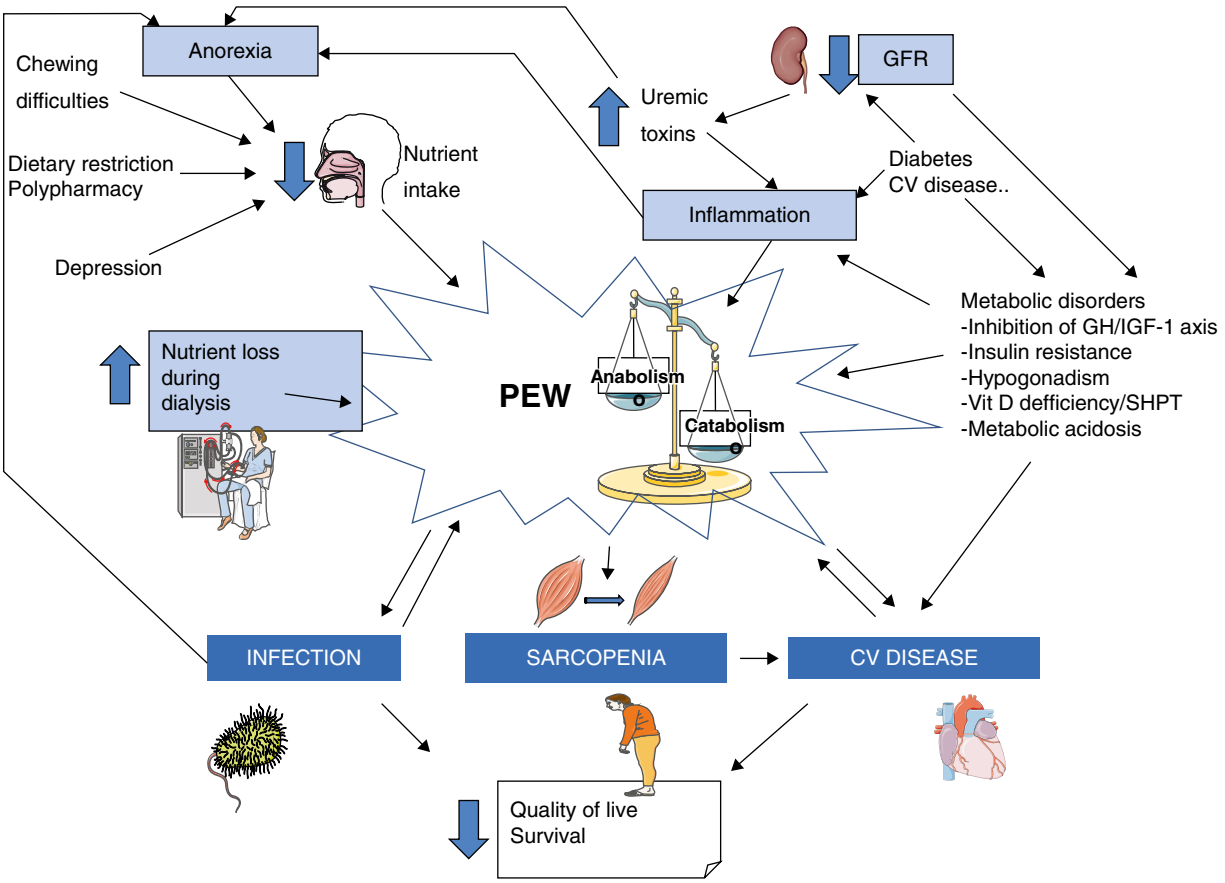

Figure 37.5 Pathophysiology of PEW. CV, cardiovascular; GFR, glomerular filtration rate; GH, growth hormone; IGF-1, insulin-like growth factor 1; PEW, protein-energy wasting; SHPT, secondary hyperparathyroidism. *Source:* Adapted from: Carrero et al. [37].

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electrolytes, as well as the use of phosphate binders during meals alter the palatability of food and its absorption, which contributes to undernutrition of this population. Even restricting fluids to reduce interdialytic weight gain in dialysis patients can decrease caloric intake, since many solid foods have a high water content.

Oral and gastrointestinal tract problems modify the quantity and quality of the food ingested. Some of these factors are very frequent, such as dry mucous membranes, glossitis, mucosal inflammation, and palatability problems; these can create difficulties in swallowing and food perception. Periodontitis and lack of teeth can make chewing difficult, forcing the patient to choose foods that are easy to chew and possibly of poor nutritional value, especially fiber [92].

Finally, psychological and social aspects such as depression, loneliness, or limited ability to perform activities of daily living also contribute to potential anorexia or difficulty in ensuring food availability [37].

Catabolic Effect of Uremia, Decreased Anabolism, and Comorbidities of the CKD Patient

Hypercatabolism is the other main component of PEW [20, 37]. Potential causes of its occurrence include the accumulation of uremic toxins, microinflammation, and metabolic alterations associated with the uremic milieu and the patient's comorbidities. Systemic inflammation contributes to PEW syndrome in CKD patients through multiple mechanisms (Figure 37.6) [93–95]. In addition to inducing reduced appetite, inflammation generates increased energy expenditure and exerts direct and indirect catabolic effects. Tumor necrosis factor alpha (TNFα) promotes the loss of lean mass through the promotion of catabolic pathways, such as nuclear factor kappa B (NF-kB) and the ubiquitin-proteasome system. Indirectly, interleukin-6 (IL-6) promotes muscle catabolism by contributing to the inhibition and resistance of anabolic pathways.

The inhibition of the GH/IGF-1 axis (due to a lower expression of IGF-1 receptors in the muscle and negative hypothalamic feedback secondary to the retention of GH, IGF-1, and its carrier protein), the resistance to insulin, and the inhibition of testosterone synthesis are the main altered anabolic pathways in CKD patients, which generates a reduction in muscle mass and strength [96, 97]. Metabolic acidosis contributes to protein hypercatabolism, mainly by activating the ubiquitin–proteasome system and other muscle proteolytic pathways, decreasing hepatic synthesis of albumin, and increasing insulin resistance, which in kidney failure is preferentially muscular, favoring the onset of sarcopenic obesity [98, 99]. Finally, the typical comorbidity of the CKD patient also contributes to hypercatabolism through several factors including anemia, water overload, cardiovascular disease, or SHPT (Figure 37.7) [37]. The coexistence of diabetes is especially relevant, given

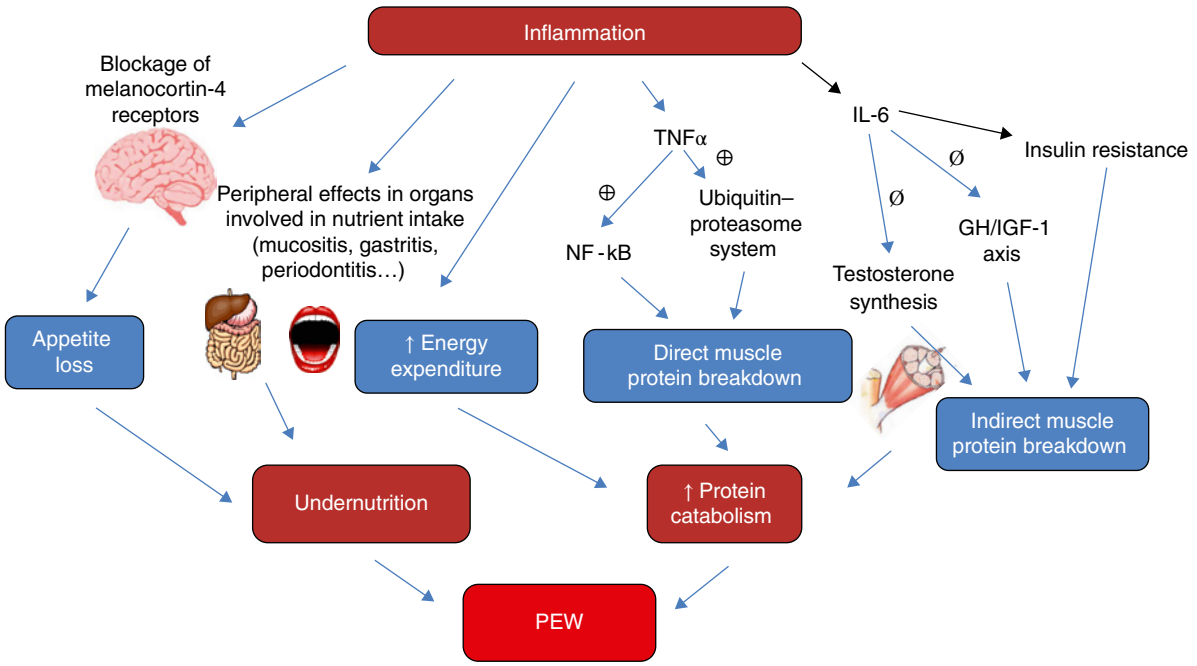

Figure 37.6 Effects of inflammation in the development of PEW. GH, growth hormone; IL-6, interleukin-6; IGF-1, insulin-like growth factor-1; NF-κB, nuclear factor kappa B; PEW, protein-energy wasting; TNFα, tumor necrosis factor alpha. *Source:* Adapted from: Lecker SH et al. [93] and Carrero et al. [94].

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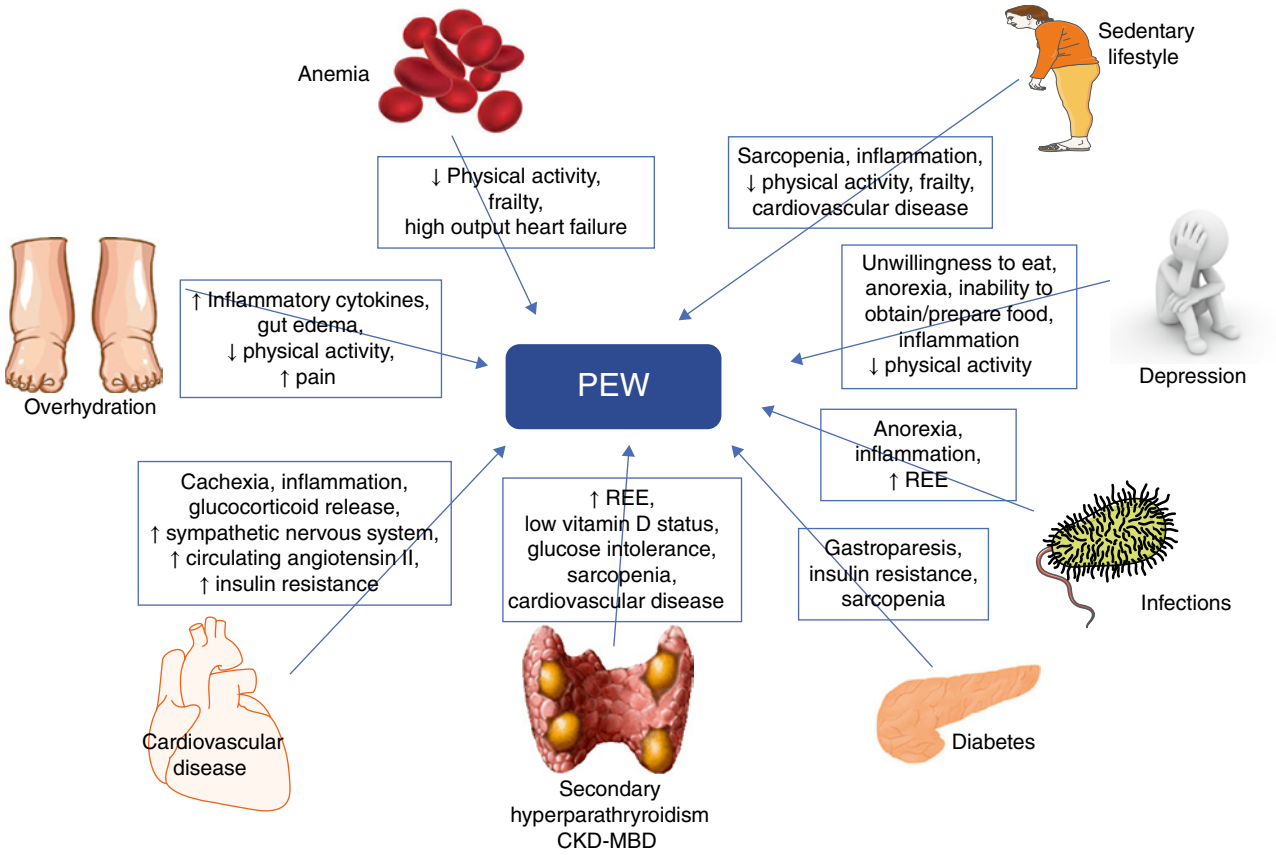

Figure 37.7 Comorbidities linked to CKD that contribute to PEW. CKD, chronic kidney disease; CKD-MBD, chronic kidney disease-mineral and bone disorder; PEW, protein-energy wasting; REE, resting energy expenditure. *Source:* Adapted from: Carrero et al. [37].

that it is associated with gastroparesis, obesity, and muscle loss with relative preservation of fat mass.

Loss of Nutrients and Catabolic Effects of Dialysis

The loss of nutrients and the inflammatory stimulus produced during dialysis contribute to the appearance of PEW. The dialysis procedure is a perfect example of the integration of malnutrition and catabolism and how PEW is carried out (Figure 37.8). Amino acids, peptides, and proteins are lost through the dialysate in both HD and PD. Plasma amino acid concentrations are reduced approximately 20% on average after a single HD session, which decreases the availability of substrate for the synthesis of muscle proteins. All this, along with the decrease in nutrient intake, leads to a lower availability of nutrients, which generates undernutrition and an increase in protein catabolism with the breakdown of muscle proteins to compensate for these losses, which contributes to the appearance of PEW [27, 37, 101–104].

Patients undergoing PD have additional characteristics inherent to the technique that modify their nutritional status, including forced absorption of glucose, which provides 300–600 kcal/day, greater protein losses by the dialysate than in HD, which can contribute to development of sarcopenic obesity, and difficult gastric emptying, which may limit the intake of food and supplements due to early satiety [105–108].

The dialysis procedure produces an inflammatory stimulus with cytokine activation, which increases muscle degradation and PEW, especially if the microbiological quality of the dialysate is low, if the membrane is bioincompatible, or if the filters are reused. Finally, patients on HD are at greater risk of loss of residual renal function, especially if high ultrafiltration rate is prescribed, which is associated with decreased appetite and an increase in basal metabolism and inflammation, aggravating PEW [37]. Both volume and a high ultrafiltration rate may also generate intestinal hypoxia by a mechanism similar to that which occurs with intradialytic myocardial stunning. This hypoxia increases the permeability of the intestinal mucosa to bacterial lipo-saccharides, favoring its translocation into the enterocyte and increasing the inflammatory state [109, 110].

The combination of hypermetabolism and undernutrition may explain why standard HD does not prevent the appearance of PEW. Although initially HD improves the appetite of the incident patients and a progressive increase

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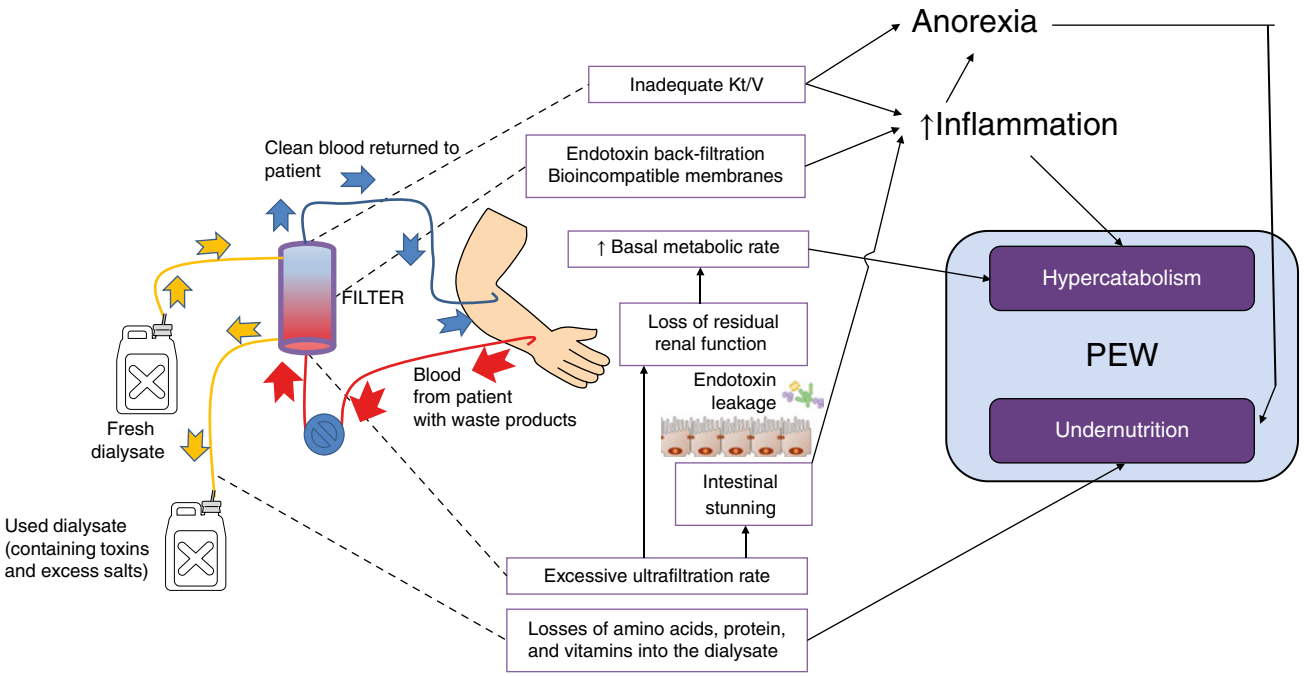

Figure 37.8 Effects of dialysis-related factors in the development of PEW. PEW, protein-energy wasting. *Source:* Adapted from: Laville and Fouque [100].

in dry weight can be observed, this increase in weight is due to the increase in fat deposits, while the muscle mass decreases progressively as the patient remains in this modality of renal replacement therapy [111].

Diagnosis: Assessment of Nutritional Status

The nutritional assessment of CKD patients requires combining different dietary, anthropometric, and biochemical criteria. Due to the lack of reference values of many of these nutritional markers for this population, it is advisable to make repeated measurements of the different markers to assess their trend over time and to be able to detect subtle changes in nutritional status. Overhydration is another issue for assessment of nutritional status, as it increases the intra- and interindividual variability of these measures [20].

To date, there are no systematic summaries of screening and diagnostic tests to evaluate nutritional status among CKD patients.

Patient Interview

The clinical history allows collection of key information related to nutritional status, including: the presence of symptoms such as nausea, vomiting, or involuntary weight loss, which are associated with high risk for PEW, treatments that can affect nutritional status, such as phosphate binders or the use of corticosteroids, and the comorbidities and the socioeconomic status of the patient [112]. In addition, the presence of proteinuria, the residual renal function, and the type of dialysis are factors that may affect the nutritional status of CKD patients.

Measures that can be routinely collected under daily practice conditions are included in the so-called screening tools. Questions that are common to all screening tools include asking about appetite and involuntary body weight changes within a given time frame. Screening tools are inexpensive and quick and easy to use, so they can be performed by any healthcare professional with the result of identifying patients who are at risk for poor nutritional status and may require further assessment [112]. Typical screening tools are the Nutrition Screening Tool, Mini-Nutrition Assessment, and Malnutrition Universal Screening Tool/Malnutrition Screening Tool. There are a few studies that have assessed their reliability in CKD patients, observing a moderate sensitivity [113, 114]. Overall, evidence for recommending the use of screening tools among CKD populations is very limited.

Anthropometry and Body Composition

Weight and Body Mass Index

These measures have the advantages of simplicity and low cost, but they do not distinguish the different body

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components (water, muscle, or fat). For HD patients, weight should always be assessed post-dialysis, taking into account the possible overhydration of the patient [115].

Mid-arm Circumference

This measure is simple to perform, correlating well with lean mass [116].

Skinfold Thickness

Subcutaneous fat evaluation by skinfold thickness of tricipital or bicipital and subscapular folds allows estimating the fat mass in adults with CKD stages 1–5 and post-transplant with a high correlation with dual energy X-ray absorptiometry (DEXA). Therefore, it is postulated as the method of choice for evaluating body fat among CKD populations [117, 118].

Bioelectrical Impedance Analysis

Bioelectrical impedance analysis (BIA) determines the electrical impedance or the resistance to the flow of an electrical current through the tissues of the body. Due to its water and electrolyte content, lean tissue is a good electrical conductor, while fat, bone, and skin are very poor conductors and offer a high resistance to electric currents. Using algorithms, BIA can calculate body water, body fat, and fat-free mass. Advantages include its ease of use and portability, as well as its sensitivity to detect changes in the short-term; it is highly recommended that BIA be available in all dialysis units. However, consideration must be given to limitations due to the state of hydration of the patient; overhydration, so frequent in CKD patients, overestimates lean mass and underestimates fat mass. Thus, repeated measures should be taken at a constant time post-dialysis to obtain a more reliable assessment of body composition with BIA [112, 119].

Handgrip Strength

This measure is a surrogate marker of lean body mass and is an indicator of superior strength of the body muscle. It has higher correlations with nutritional status and inflammatory markers, and was more predictive of mortality than muscle mass measured by DEXA. Its limitations are the lack of standardized protocols (with respect to body posture, selection/position of the hand) and the lack of reference measurements in the CKD population [116, 120, 121].

Nutritional Assessment Scores

Subjective Global Assessment

Subjective Global Assessment (SGA) is the most used nutritional questionnaire in CKD patients, and combines subjective clinical findings and objectives of the clinical history and physical examination to obtain a score that classifies the nutritional status of the patient from well-nourished to very malnourished. It collects information on weight changes, dietary intake, persistent gastrointestinal symptoms, functional capacity, nutritional needs, and physical examination [104]. It takes 15 minutes to complete by a health professional who has been trained to perform it. Several studies have demonstrated the validity and reliability of the 7-point SGA score among CKD patients (including ND-CKD, HD, and PD) and its correlation with other measures of nutritional status, including lean body mass and serum albumin levels [122–125].

Malnutrition-Inflammation Score

Malnutrition-Inflammation Score (MIS) is a modified version of the SGA, and incorporates three new objective parameters: body mass index (BMI), serum albumin, and transferrin or iron binding capacity. It was designed in an attempt to reduce the subjectivity of the SGA by using a quantitative scoring system. Each of the referred items are scored from 0 to 3. A MIS score of 0–5 is considered normal, 6–17 represents mild/moderate malnutrition, and 18–30 indicates severe malnutrition. MIS was designed specifically for the HD population [126], although it has also been validated in ND-CKD, PD, and kidney transplant patients [127–129].

Biochemistry

Albumin

Serum albumin concentration is the most used nutritional parameter in CKD patients due to its reproducibility and low cost, as well as its capacity to respond to nutritional interventions [130]. Several studies have supported that serum albumin concentration is a sensitive measure of nutritional status, being associated with other common nutritional status markers in CKD. Although evidence suggests that it is a strong predictor of mortality, it has a half-life of 20 days, which means that its response to acute changes in nutrient intake is delayed. Another limitation is its low specificity, since albumin is influenced by inflammation, stress, and overhydration [131–135]. An albumin level below 3.8 g/dl is suggestive of PEW [20].

Prealbumin

The main advantage of prealbumin (or transthyretin) is its half-life of 2 days, which makes it more sensitive to short-term changes in nutritional status and/or acute response to nutritional therapy than albumin. However, levels are affected by kidney function, inflammatory status, and intercurrent diseases [131]. Prealbumin levels below 30 mg/dl are suggestive of PEW [20].

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Serum Creatinine

This may be an adequate surrogate measure of muscle mass in dialysis patients as long as residual kidney function is minimal or absent. There are no defined cut-off points, so longitudinal assessment is suggested for each patient, with the advantage that it is useful for detecting individual changes in the short term [130, 133]. In addition, serum creatinine determination allows for the calculation of the creatinine index [135].

Creatinine Index

If bioimpedance testing is not available, lean mass can be estimated using the kinetic model of creatinine, which is a reliable method to monitor muscle mass and protein nutritional status in dialysis patients. It is based on the principle that the generation of creatinine is proportional to muscle mass in stable patients in steady state. The creatinine index is defined as the normalized creatinine production rate, which is equal to the sum of the creatinine excretion rate (creatinine in the dialysate + urinary creatinine) and the rate of metabolism of creatinine in a state of metabolic equilibrium. To avoid post-dialysis determination of blood creatinine and dialysate, different formulas have been developed to calculate the creatinine index from baseline creatinine levels, Kt/V, age, and sex [135].

Cholesterol

Although a blood cholesterol level of less than 100 mg/dl is a criterion for PEW [3], its use as a nutritional marker is limited given that it is negatively influenced by lipid-lowering treatment and positively influenced by proteinuria [130].

C-Reactive Protein

Although not a nutritional parameter, the determination of serum levels of C-reactive protein (CRP) allows monitoring of the inflammatory state in the CKD patient in a reproducible way. Given the great variability of CRP, repeated testing is required to assess its trend in each patient [130].

Protein Equivalent of Nitrogen Appearance

The kinetic model of urea has been used to estimate protein intake in HD patients in a steady state [133]. The protein equivalent of nitrogen appearance (PNA or nPCR) is calculated based on the increase of nitrogen in the interdialysis period. Catabolic or anabolic processes may overestimate or underestimate, respectively, the measurement of protein intake by this method. If the patient has residual kidney function, the urea lost in the urine should be taken into account [130]. For ND-CKD patients, protein intake may be estimated from urinary urea excretion with Maroni's formula [136].

Assessment of Food Intake

There are three methods to assess the food intake of proteins, calories, and nutrients in CKD patients. This should be done periodically and/or whenever PEW is suspected.

Twenty-four-hour Dietary Recalls

Through an interview, the patient is asked to recall food intake during the previous 24 hours. The main limitation of this method is that it extrapolates the intake of a day as the habitual intake of the patient, together with the high risk of bias, especially when the patient may have cognitive disorders or is not cooperative. The main advantages are the speed of its execution (it can even be done by telephone) and the lack of need for record-keeping by the patient [137–139].

Food Diaries and Records

The patient (or caregiver) is required to record food intake for 3 or 7 days, including a day of HD if this is the case and a weekend day. From this, a dietitian estimates the patient's food intake from food composition tables with the help of computer programs [140]. The most important limitations are food intake not recorded completely or accurately, and the impossibility of detecting seasonal variations in intake [137].

Food Frequency Questionnaires

In these, a series of questions ask about the frequency and amount of consumption of several common foods during the last 6–12 months; calculation of the amount of food ingested is done by multiplying the frequency by the specific amount for the measure provided. With questions such as "How many times a week do you eat fruit?", it may be easier to perform than the 3- or 7-day food diary, although it is not as reliable as such records [140]. One advantage is that it gives a view of food intake over a longer period of time, which is why it is especially useful in epidemiological studies. However, it is of little use at the individual level or when analyzing small groups of patients [137].

Assessment of Resting Energy Expenditure

Knowledge concerning energy requirements of CKD patients is imperative to providing a sufficient amount of energy to maintain adequate nutritional status [141]. Although indirect calorimetry is the most accurate method for measuring resting energy expenditure (REE), it is not usually available in the clinical routine [142]. In the absence of indirect calorimetry, several predictive energy equations based on simple bedside parameters have been

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proposed. However, it must be noted that prediction equations used in normal individuals (i.e. Harris and Benedict's equation) overestimate REE in the ND-CKD population, although the errors may be minimized in the presence of comorbidities [142]. Conversely, several equations have been specifically developed for dialysis patients and validated in this population [143].

Prognosis: Consequences of PEW in Mortality, Morbidity, and Quality of Life

Multiple observational studies have shown that PEW markers are independently associated with worse survival [39, 144–146], decreased quality of life [147], increased risk of infections, and complications related to cardiovascular disease, with greater risk of hospitalization and healthcare costs [148, 149]. Moreover, the consequences of PEW are so rapid and negative in the prognosis of CKD patients that this modifies the usual and logical relationship between risk factors and poor evolution [150]. A clear example is the association between surrogates of overnutrition (i.e. obesity or hyperlipidemia) and mortality. In dialysis patients, obesity (versus normal weight) is associated with better survival, whereas the opposite effect is observed in the general population. The most likely explanation is that patients undergoing dialysis usually die from the short-term consequences of PEW and do not live long enough to die of cardiovascular disease associated with obesity. Additionally, increased fat deposits could protect the PEW patient for longer [151].

Although RCTs demonstrating the causal association between undernutrition and hypermetabolism with adverse patient outcomes in CKD patients are lacking, several epidemiological studies have explored this issue, showing that nutritional interventions in hypoalbuminemic HD patients may be effective in reducing hospitalizations rates and mortality [152–154]. All these data support the hypothesis that PEW is not only a risk factor, but also a treatable etiological factor in preventing mortality and morbidity, so that nutritional therapy can result in multiple improved clinical outcomes throughout the spectrum of CKD.

Treatment

People with kidney disease represent an extremely heterogeneous group of patients in whom nutritional recommendations may differ greatly depending on the type of nephropathy, its form of onset (acute or chronic), and the therapeutic goals being pursued, as, for example slowing down progression in the patient with ND-CKD, alleviating the protein hypercatabolism associated with the uremic milieu in the dialysis patient, or controlling the hyperkalemia in the patient under conservative treatment.

Although extensive literature has shown that high mortality risk in CKD patients is related in part to the nutritional derangements linked to kidney failure, there is not enough evidence to address the exact role of different dietary interventions in the prognosis of the CKD population. Whereas undernutrition may increase the risk for PEW, overnutrition may lead to sodium and volume overload, high BP, hyperkalemia, hyperphosphatemia, and accumulation of toxic metabolites of protein degradation. Treatment to decrease proteinuria and BP and improve several markers of PEW, such as serum albumin levels, have demonstrated efficacy across many RCTs, while evidence to hard clinical outcomes including survival, cardiovascular events, or CKD progression remains inconclusive. However, this lack of evidence does not necessarily indicate that nutritional interventions have no effect on CKD outcomes. Moreover, given that nutritional therapy including dietary counseling and supplements is safe and cost-effective, it should be considered to improve the poor prognosis of CKD patients.

Dietary Interventions for Survival, Quality of Life, and Overall Health of Adults with CKD

Dietary interventions are routinely recommended in CKD patients given the potential ability to influence clinical outcomes in this population. On the basis of evidence from nonrandomized studies in CKD patients, and especially from randomized studies in the general population, it has been suggested that healthy dietary patterns may prevent hard outcomes, including survival, cardiovascular events, and health-related quality of life [155].

However, the optimal approach to nutrition in CKD patients is not well known, and the few RCTs conducted in this population have yielded conflicting results. In 2017, a Cochrane review evaluated the benefits and harms of dietary interventions in CKD patients, including dietary patterns and nutritional counseling, with all-cause mortality, major adverse cardiovascular events, and health-related quality of life being the primary outcomes [1]. The review evaluated 17 RCTs with 1639 adult CKD patients, including 10 studies with 1130 people with ND-CKD stages 1–5, three studies with 341 dialysis patients, and four studies with 168 kidney transplant recipients (summarized in Table 37.4). Eleven studies ($n = 900$) evaluated dietary counseling and six studies evaluated dietary patterns ($n = 739$), including the Mediterranean diet (two studies, $n = 355$), a carbohydrate-restricted, low-iron, polyphenol-enriched diet

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Table 37.4 Summary of findings: dietary interventions for overall health of adults with CKD.

Outcomes	No. of participants (no. of studies)	Absolute number of patients affected per 1000 patients treated for one year (95% CI)	Relative effect (95% CI)[a]	Certainty of the evidence (GRADE)	Conclusion
Primary outcomes					
Death (all causes): dietary counseling	371 (4)	Not estimable	1.59 (0.60–4.21)	Very low ●○○○	It is uncertain whether dietary counseling impacts on all-cause mortality
Death (all causes): CR-LIPE diet	170 (1)	Not estimable	0.50 (0.22–1.12)	Very low ●○○○	It is uncertain whether CR-LIPE diet impacts on all-cause mortality
Major adverse cardiovascular events: dietary counseling	62 (1)	Not estimable	6.58 (0.35–122.21)	Very low ●○○○	It is uncertain whether dietary counseling impacts on major adverse cardiovascular events
Health-related quality of life: dietary counseling	119 (2)	—	The MD in SF-36 score was 11.46 higher (7.73 higher to 15.18 higher) in the intervention groups compared to control	Low ●●○○	Dietary counseling may have clinically important increases in the SF-36 quality of life score
Secondary outcomes					
ESRD: dietary counseling and CR-LIPE diet	232 (2)	0.3 fewer (1 person in every 3000 treated for one year avoiding ESRD)	0.53 (0.26–1.07)	Very low ●○○○	It is uncertain whether dietary interventions impact on risks of ESRD
Worsening nutrition (subjective global assessment): dietary counseling	230 (2)	Not estimable	0.40 (0.05–3.37)	Very low ●○○○	It is uncertain whether dietary counseling impacts on risks of worsening nutrition as measured by subjective global assessment
eGFR: dietary counseling, Mediterranean diet, and fruits and vegetables	219 (5)	—	The SMD in eGFR was 1.08 higher (0.20 higher to 1.97 higher) with dietary intervention compared to standard care	Very low ●○○○	Dietary interventions may increase eGFR
Serum creatinine: dietary counseling and Mediterranean diet	112 (3)	—	The MD in creatinine was 0.83 μmol/l higher (−16.57 lower to 18.23 higher) with dietary intervention compared to standard care	Very low ●○○○	It is uncertain whether dietary interventions impact on creatinine levels
Systolic blood pressure: dietary counseling and fruits and vegetables	167 (3)	—	The MD in systolic BP was −9.26 mmHg lower (−13.48 lower to −5.04 lower) with dietary intervention compared to standard care	Moderate ●●●○	Dietary interventions probably reduce systolic BP

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Diastolic blood pressure: dietary counseling	95 (2)	—	The MD in diastolic BP was −8.95 mmHg lower (−10.69 lower to −7.21 lower) with dietary intervention compared to standard care	Moderate ●●●○	Dietary counseling probably reduces diastolic BP
Energy intake: dietary counseling	340 (4)	—	The SMD in energy intake was 1.54 higher (−0.87 lower to 3.95 higher) with dietary intervention compared to standard care	Very low ●○○○	It is uncertain whether dietary counseling impacts on energy intake
Energy intake: Mediterranean diet	40 (1)	—	The SMD in energy intake was 1.86 higher (1.11 higher to 2.61 higher) with Mediterranean diet compared to standard care	Very low ●○○○	Mediterranean diet may increase energy intake
Energy intake: high nitrogen and low carbohydrate diet	12 (1)	—	The SMD in energy intake was −0.65 lower (−1.82 lower to 0.53 higher) with high nitrogen and low carbohydrate diet compared to standard care	Very low ●○○○	It is uncertain whether high nitrogen and low carbohydrate diet impacts on energy intake
Body weight: dietary counseling, fruits and vegetables, CR-LIPE, and high nitrogen and low carbohydrate diet	454 (6)	—	The MD in body weight was −0.44 kg lower (−1.46 lower to 0.58 higher) with dietary intervention compared to standard care	Very low ●○○○	It is uncertain whether dietary interventions impact on body weight
BMI: dietary counseling	119 (2)	—	The MD in BMI was −1.70 kg/m^2 lower (−5.23 lower to 1.82 higher) with dietary intervention compared to standard care	Very low ●○○○	It is uncertain whether dietary counseling impacts on BMI
Arm circumference: dietary counseling	149 (2)	—	The MD in arm circumference was 0.37 higher (−0.39 lower to 1.12 higher) with dietary intervention compared to standard care	Very low ●○○○	It is uncertain whether dietary counseling impacts on arm circumference
Serum albumin: dietary counseling, Mediterranean diet, and CR-LIPE	541 (6)	—	The MD for the effect of serum albumin levels was 0.16 mg/dl higher (0.07 higher to 0.24 higher) with dietary intervention compared to control or standard care	Low ●●○○	Dietary interventions may increase albumin levels

BMI, body mass index; BP, blood pressure; CR-LIPE, carbohydrate-restricted, low-iron-available, polyphenol-enriched; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; SF-36, short-form 36-item health survey.

Treatment estimates are drawn from a Cochrane review [1]. GRADE assessment of the certainty of the evidence [17]: High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different* is low. Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different* is moderate. Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different* is high. Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different* is very high. *Substantially different = a large enough difference that it might affect decision-making.

[a] Effects are reported as the relative risk (RR) and 95% confidence interval (CI) for binary outcomes and mean difference (MD) and 95% CI for continuous outcomes (standardized mean difference [SMD] if different scales were used).

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(one study, $n = 191$), increased fruit and vegetable intake (two studies, $n = 181$), and a high protein/low carbohydrate diet (one study, $n = 12$). Studies related to dietary management of specific dietary factors such as protein, sodium, or phosphate were excluded. According to this systematic review, dietary interventions have uncertain effects on mortality and cardiovascular events among CKD patients as studies were not designed to examine these outcomes. In very-low-quality evidence, dietary interventions had uncertain effects on the development of end-stage renal disease (ESRD). Conversely, dietary interventions may increase health-related quality of life, eGFR, and serum albumin, and reduce several risks factors for cardiovascular events such as BP and serum LDL cholesterol levels. Whether these favorable effects on these surrogate endpoints would improve clinical outcomes for CKD patients remains uncertain [1].

Nutritional Interventions to Slow Progression of CKD

Dietary Protein Restriction

According to the hyperfiltration theory, the amount of protein intake in current diets, which is generally higher than our daily needs, could explain the appearance of glomerular sclerosis that accompanies aging (0.75–1.5 ml/min/year from the age of 40) [156–159]. Conversely, dietary protein restriction may protect against CKD progression by hemodynamic-mediated mechanisms, including intraglomerular pressure reduction, as well as by changes in cytokine expression and matrix synthesis (Figure 37.2) [62].

Nearly 20 RCTs have assessed the effects of protein restriction on kidney outcomes of interest, including CKD progression and the need for maintenance dialysis, proteinuria, phosphate levels, acidemia, and BP. These studies have been summarized in several meta-analyses [2–5, 160–165]. Most of these have been conducted recently [2–4], which indicates there remains great interest regarding protein restriction in CKD patients [62, 166, 167].

Several practical approaches have been described for protein restriction, with 0.6–0.8 g/kg of weight per day (LPD) being most frequently recommended for ND-CKD patients stages 3–5. However, a greater restriction of less than 0.6 g/kg/day (VLPD) supplemented with essential amino acids or their ketoacids has also been tested. The safety and implementation of protein restriction diets should be accompanied by ensuring adequate energy intake (30–35 kcal/kg/day) and regular nutritional checks. Overall, the balance of evidence suggests a benefit of dietary protein restriction (summarized in Table 37.5).

However, results of some RCTs have not consistently demonstrated that protein restriction would be beneficial in CKD progression. The primary results of the largest trial to date, the Modification of Diet in Renal Disease (MDRD), which analyzed the effect of protein restriction and intensive control of BP on the rate of loss of GFR (measured by iothalamate clearance) in 840 ND-CKD patients, did not support the hypothesis of benefit of protein restriction on the progression of kidney failure [168]. It is possible that the MDRD study duration was too short to fully appreciate the effect of protein restriction; this and other limitations could have allowed classifying this RCT as inconclusive rather than negative [169]. Indeed, subsequent secondary analyses performed by some of the MDRD investigators concluded that the balance of evidence was more consistent with the hypothesis of beneficial effect from the reduction of the proteins in the diet rather than with the hypothesis of nonbenefit, with this benefit being additive to that obtained by the BP control. The restriction of proteins slowed the deterioration of GFR, mainly in more advanced stages and in those cases of more rapid loss of renal function. These findings would justify the recommendation of an LPD in ND-CKD patients, and its safety, when accompanied by nutritional advice and systematic monitoring, is also supported by the evidence [169, 170].

In 2007 and 2018, two Cochrane reviews summarized the evidence for protein restriction for diabetic and nondiabetic kidney diseases, respectively [3, 5]. A summary of the findings is shown in Table 37.6. Evidence for beneficial effects of protein restriction for nondiabetic patients with ND-CKD stages 3–5 is restricted to effects of VLPD on progression to ESRD. Conversely, when LPDs were compared with normal protein diets, there was little or no difference in the number of people who progressed to dialysis. LPDs or VLPDs probably do not influence death; however, there are limited data on other adverse effects such as weight differences and PEW. Most studies reported that adherence to diet was satisfactory, but quality of life was not formally assessed in any studies. The authors encouraged conduct of new studies evaluating the adverse effects and the impact on quality of life of dietary protein restriction before these dietary approaches be recommended for widespread use [3].

Restricted protein intake appeared to slow progression of diabetic kidney disease, but not by much on average. Only one study explored all-cause mortality and ESRD as endpoints in type 1 diabetic patients, showing a relative risk (RR) of 0.23 for patients assigned to LPD. However, pooling of the seven RCTs of patients with type 1 diabetes resulted in a nonsignificant reduction in the decline of GFR of 0.1 ml/min/month (95% confidence interval [CI] −0.1 to 0.3) in the LPD group. For type 2 diabetes, one trial showed a small insignificant improvement in the rate of decline of GFR in the protein-restricted group and a second found a

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Table 37.5 Meta-analyses and systematic reviews of diet protein restriction for kidney outcomes (RCTs only).

Author	No. of studies	Sample	Outcome measures	Methods	Conclusions
Fouque et al. [160]	6	$n = 890$ ND-CKD with varying degrees of renal failure	No. of deaths due to renal cause or need to initiate hemodialysis treatment	Difference in protein intake >0.2 g/kg/day in both groups Follow-up of at least 1 year	LPDs slowed progression to ESRD.
Pedrini et al. [161]	5	$n = 1413$ ND-CKD with moderate degree of renal failure	Calculation of RR of progression of renal disease	LPD of 0.4–0.6 g/kg/day Follow-up for 18–36 months	Protein restriction slowed progression of renal disease in diabetic and nondiabetic patients
Kasiske et al. [162]	13	$n = 1919$ ND-CKD (degree of renal failure was unreported)	Differences in rate of fall of GFR or creatinine clearance between control groups and groups treated with LPDs	Measurement of protein intake with urea excretion and nitrogen Analysis of results by intent-to-treat Measurement of disease progression by GFR or creatinine clearance Follow-up for 6–36 months	Protein restriction reduced the rate of decline in eGFR, although the magnitude of effects was weak [by only 0.53 ml/min/year (95% CI 0.08–0.98 ml/min/year)] The effect of dietary protein restriction was relatively greater among diabetic versus nondiabetic patients (5.4 ml/min/year, 95% CI 0.3–10.5 ml/min/year, $P < 0.05$)
Fouque et al. [163]	7	$n = 1494$ ND-CKD stages 3–5 Only nondiabetic patients	Renal death (death of any cause, requirement to start dialysis, or kidney transplant)	In theory, difference in protein intake between higher and restricted protein intake groups was approximately 0.35 g/kg/day in almost all the studies. However, based on urinary collection of protein waste products, the actual reduction in protein intake between groups in each study was less than expected (between 0.2 and 0.35 g/kg/day). Follow-up of at least 1 year	Reducing protein intake overall reduced renal deaths by about 39% ($P = 0.006$) To spare one extra renal death, 17 patients need to be treated with a low protein diet for approximately 2 years A subgroup analysis of the "start of dialysis" event was also highly significant, with an OR of 0.56 in favor of a restricted protein intake ($P < 0.01$)
Robertson et al. [5]	12 (nine RCTs, three before and after studies)	$n = 585$ Only diabetic patients (type 1 : 322; type 2 : 263) with nephropathy (UAER ≥300 mg/day)	Biochemistry (GFR), ESRD (all-cause mortality, nutritional status, health-related QOL, and costs were also analyzed)	Actual protein intake in the intervention groups ranged from 0.7 to 1.1 g/kg/day Interventions of reduced or modified protein intake ≥4 months	The RR of ESRD or death was 0.23 (95% CI 0.07–0.72) for patients assigned to an LPD Pooling of the seven RCTs in patients with type 1 diabetes resulted in a nonsignificant reduction in the decline of GFR of 0.1 ml/min/months (95% CI −0.1 to 0.3) in the LPD group For type 2 diabetes, one trial showed a small insignificant improvement in the rate of decline of GFR in the protein-restricted group and a second found a similar decline in both the intervention and control groups A specific recommendation of the necessary protein level to achieve this outcome was not possible

(*Continued*)

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Table 37.5 (Continued)

Author	No. of studies	Sample	Outcome measures	Methods	Conclusions
Fouque et al. [165]	10 (also included three crossover studies)	$n = 1494$ CKD stages 3–5 Only nondiabetic patients	Renal death (death of any cause, requirement to start dialysis, or kidney transplant)	Protein intake (≥0.8 g/kg/day) vs. moderate (0.6 g/kg/day) to severe protein restriction (0.3 g/kg/day) regardless of supplementation with amino acids or keto-acids	Reducing protein intake overall reduced renal deaths by about 32% ($P = 0.0002$) Subanalysis (seven studies) found that reduced protein intakes between 0.3 and 0.6 g/kg/day compared to higher/free protein intakes resulted in a significant reduction in renal deaths (37%, $P = 0.0009$) The optimal level of protein intake cannot be determined based on this review
Rughooputh et al. [166]	15	$n = 1965$ CKD stages 1–5	Change in mean GFR	The assessment of protein intake was based on reported urinary indices Pooling the mean values for all studies, the achieved protein intake was 0.83 (0.15) g/kg/day in the experimental arm and 1.07 (0.17) g/kg/day in the control arm, based solely on urinary indices Follow-up of at least 1 year	Moderate protein diet restriction slowed CKD progression in nondiabetic and type 1 diabetic patients (−1.50 ml/min/1.73 m^2/year, 95% CI −2.73 to 0.26, $P = 0.0175$), but not in type 2 diabetic patients (−0.17 ml/min/1.73 m^2/year, 95% CI −1.88 to 1.55, $P = 0.85$)
Rhee et al. [2]	16 (RCTs with less than 30 participants were excluded)	$n = 2771$ CKD stages 3–5 (one study with 60 new ESRD patients on peritoneal dialysis with residual kidney function was also included)	Rate of progression to ESRD (all-cause mortality, nutritional status, and bicarbonate and phosphorus levels were also analyzed)	LPD (<0.8 g/kg/day) vs. higher protein diets (>0.8 g/kg/day) VLPD (<0.4 mg/kg/day) vs. LPD (0.4–0.8 mg/kg/day)	Risk of progression to ESRD was 4% lower in those who received LPD LPD (<0.8 g/kg/day) was also associated with higher serum bicarbonate levels, lower phosphorus levels, lower azotemia, and a trend toward lower rates of all-cause mortality VLPDs (protein intake <0.4 g/kg/day) were associated with greater preservation of kidney function and reduction in the rate of progression to ESRD Safety and adherence to a LPD was not inferior to a normal protein diet, and there was no difference in the rate of malnutrition or protein-energy wasting

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Hahn et al. [3]	17	$n = 2996$ ND-CKD stages 3–5	End or change in GFR, ESRD (all-cause mortality and nutritional status were also analyzed)	LPD (0.5–0.6 g/kg/day) compared with a normal protein intake (≥0.8 g/kg/day) VLPD (0.3–0.4 g/kg/day) compared with LPD (0.5–0.6 g/kg/day) Follow-up of at least 1 year	LPD compared with a normal protein intake did not impact on the incidence of ESRD (RR 1.05, 95% CI 0.73–1.53) and on the outcome of final or change in GFR (SMD −0.18, 95% CI −0.75 to 0.38) VLPD comparted with LPD reduced the number who reach ESRD (RR 0.65, 95% CI 0.49–0.85) with no influence on the final or change in GFR (SMD 0.12, 95% CI −0.27 to 0.52) It was uncertain whether LPD or VLPD alter survival Twelve studies reported no evidence of protein-energy wasting in their study participants, while three studies reported small numbers of participants in each group with protein-energy wasting. It was uncertain whether LPD or VLPD alter final body weight. Most studies reported that adherence to diet was satisfactory Quality of life was not formally assessed in any studies
Yan et al. [4]	19	$n = 2492$ CKD stages 1–5 (two studies with 78 and 60 peritoneal dialysis patients were also included)	Kidney failure events, rate of change in eGFR per year, and changes in proteinuria (all-cause mortality, nutritional status, and phosphorus levels were also analyzed)	The difference in protein intake between protein restriction and control groups was at least 0.2 g/kg/day Follow-up of at least 24 weeks	LPD reduced the risk of kidney failure (OR = 0.59, 95% CI 0.41–0.85) and ESRD (OR = 0.64, 95% CI 0.43–0.96), but did not produce a clear beneficial effect for all-cause death events (OR = 1.17, 95% CI 0.67–2.06) The change in the MD for the rate of decline in the eGFR was significant (MD −1.85, $P = 0.001$), and for the proteinuria reduction (MD −0.44, $P = 0.02$) LPD also reduced the serum phosphorus concentration (MD −0.37, 95% CI −0.5 to −0.24) and BMI (MD −0.61, 95% CI −1.05 to −0.17). However, the change in albumin presented no significant difference between two groups (MD 0.23, 95% CI −0.51 to 0.97).

BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease, ESRD, end-stage renal disease; eGFR, estimated glomerular filtration rate; LPD, low protein diet; MD, mean difference; ND-CKD, nondialysis chronic kidney disease; OR, odds ratio; QOL, quality of life; RCT, randomized controlled trial; RR, relative risk; SMD, standardized mean difference; UAER, urinary albumin excretion rate; VLDP, very-low protein diet. *Source:* Hahn D, Hodson EM, Fouque D (2018); Robertson L, Waugh N, Robertson A.(2007); Hultcrantz M et al.(2017).

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Table 37.6 Summary of findings: dietary protein restriction for adults with CKD.

Outcomes	No. of participants (no. of studies)	Absolute number of patients affected per 1000 patients treated for one year (95% CI)	Relative effect (95% CI)[a]	Certainty of the evidence (GRADE)	Conclusion
Low protein diet versus normal protein diet for nondiabetic adults with CKD stages 3–4					
Death (all causes)	1680 (5)	13 fewer (27 fewer to 10 more)	0.77 (0.51–1.18)	Moderate ●●●○	LPD probably does not influence death
ESRD	1814 (6)	7 more (39 fewer to 76 more)	1.05 (0.73–1.53)	Low ●●○○	LPD may make little difference to the number of people who progress to ESRD
End of study or change in GFR	1680 (8)	Not estimable	The SMD for end or change in GFR was 0.18 lower (0.75 lower to 0.38 higher) with LPD compared to normal protein diet	Very low ●○○○	It is uncertain whether LPD impacts on the outcome of final or change in GFR
End of study body weight	223 (2)	Not estimable	The MD for end body weight was 3.09 kg lower (5.02 lower to 1.16 lower) with LPD compared to normal protein diet	Very low ●○○○	It is uncertain whether LPD impacts on final body weight
Quality of life	—(−)	Not estimable	Not estimable	Absent	No studies were found that evaluated quality of life
Very low protein diet versus low or normal protein diet for nondiabetic adults with CKD stages 4–5					
Death (all causes)	681 (6)	10 more (15 fewer to 60 more)	1.26 (0.62–2.54)	Moderate ●●●○	VLPD compared with LPD probably makes little or no difference to death
ESRD	1010 (10)	165 fewer (69–233 fewer)	0.65 (0.49–0.85)	Moderate ●●●○	VLPD probably reduces number of people who progress to ESRD
End of study or change in GFR	456 (6)	Not estimable	The SMD for end or change in GFR was 0.12 higher (0.27 lower to 0.52 higher) with VLPD compared to LPD	Very low ●○○○	It is uncertain whether VLPD compared with LPD impacts on the outcome of final or change in GFR
End of study body weight	291 (4)	Not estimable	The MD for end body weight was 1.40 kg higher (3.40 lower to 6.21 higher) with VLPD compared to LPD	Very low ●○○○	It is uncertain whether VLPD impacts on final body weight
Development of PEW	2373 (15)	Not estimable	1.31 (0.42–4.13)	Low ●●○○	Protein restriction may make little difference to the number of people who develop PEW
Quality of life	— (−)	Not estimable	Not estimable	Absent	No studies were found that evaluated quality of life

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Low protein diet versus normal protein diet for diabetic renal disease					
Death (all causes) or ESRD: LPD vs. normal protein diet in type 1 diabetic patients	84 (1)	Not estimable	0.23 (0.07–0.72)	Low ●●○○	LPD may prevent death or progression to ESRD in type 1 diabetic patients
Change in GFR: LPD vs. normal protein diet in type 1 diabetic patients	222 (7)	Not estimable	There was a nonsignificant improvement in GFR of 0.1 ml/min/month (95% CI −0.1 to 0.3) in the LPD group	Low ●●○○	LPD may make little difference to the change in GFR in type 1 diabetic patients
Change in GFR: LPD vs. normal protein diet in type 2 diabetic patients	83 (2)	Not estimable	Not estimable	Very low ●○○○	It is uncertain whether LPD impacts on change in GFR in type 2 diabetic patients
Quality of life	— (−)	Not estimable	Not estimable	Absent	No studies were found that evaluated quality of life

CKD, chronic kidney disease; ESRD, end-stage renal disease; GFR, glomerular filtration rate; LPD, low protein diet; VLDP, very-low protein diet; PEW, protein-energy wasting.
Treatment estimates are drawn from two Cochrane reviews [3, 5]. GRADE assessment of the certainty of the evidence [17]: High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different* is low. Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different* is moderate. Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different* is high. Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different* is very high. *Substantially different = a large enough difference that it might affect decision-making.
[a] Effects are reported as the relative risk (RR) and 95% confidence interval (CI) for binary outcomes and mean difference (MD) and 95% CI for continuous outcomes (standardized mean difference [SMD] if different scales were used).
Source: Hahn D, Hodson EM, Fouque D (2018); Robertson L, Waugh N, Robertson A.(2007); Hultcrantz M et al.(2017).

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similar decline in both the intervention and control groups. No data on the effects of LPDs on health-related quality of life in this population were found. According to the authors, and due to the variability amongst patients, there might perhaps be a 6-month therapeutic trial of protein restriction in all individuals with diabetic kidney disease, with continuation only in those who responded best [5].

Dietary Salt Restriction

The restriction of salt in the diet reduces BP and reduces proteinuria (independently of the effect on the BP) by a direct effect on the renin-angiotensin-aldosterone system, potentially improving cardiovascular outcomes and CKD progression to ESRD. However, the lack of long-term RCTs assessing the effectiveness and safety of dietary salt restriction on CKD progression and survival precludes any firm conclusions [62].

A 2015 Cochrane review summarized the evidence for salt restriction from eight RCTs of 258 adults with CKD (including six studies with ND-CKD patients, one with dialysis patients, and one with kidney transplant recipients) that compared two or more levels of salt intake [6]. Unfortunately, the short follow-up of the included studies (1–26 weeks) did not allow for establishing the effect of sodium intake on primary endpoints such as cardiovascular and all-cause mortality, cardiovascular events, or CKD progression. However, low salt interventions were associated with significant reduction in 24-hour sodium excretion (range 52–141 mmol) (eight studies, 258 patients, mean difference [MD] −105.86 mmol/day, 95% CI −119.20 to −92.51), systolic BP (eight studies, 258 patients, MD −8.75 mmHg, 95% CI −11.33 to −6.16), and diastolic BP (eight studies, 258 patients, MD −3.70 mmHg, 95% CI −5.09 to −2.30), allowing a significant reduction in antihypertensive treatment dosage (two studies, 52 patients, RR 5.48, 95% CI 1.27–23.66). Although data regarding urinary protein excretion was not able to be meta-analyzed, a significant reduction in proteinuria in relation to a low salt diet was noted in all the RCTs that reported this outcome [171–174]. Salt restriction significantly increased plasma renin activity and serum aldosterone, whereas one study reported a 56% reduction in the risk of edema [171]. There was no significant change in eGFR (two studies, 68 patients, MD −1.14 ml/min/1.73 m^2, 95% CI −4.38 to 2.11) or creatinine clearance (three studies, 85 patients, MD −4.60 ml/min, 95% CI −11.78 to 2.57) in relation to low salt interventions.

The effect of moderate salt restriction for lowering BP and proteinuria was confirmed in a 2018 meta-analysis of RCTs comparing the effect of low versus high salt intake, which involved 11 studies of 738 patients with ND-CKD stages 1–4 [7].

Dietary Caloric Restriction

Among both the general population and ND-CKD patients, an extensive body of evidence from epidemiological studies indicates that obesity and central fat distribution are independent risk factors for CKD progression and the development of ESRD [175, 176]. Insulin resistance, obesity-mediated hypertension, glomerular hyperfiltration, renin-angiotensin-aldosterone system activation, glomerular hypertrophy, and inflammation are the potential mechanisms by which obesity may increase CKD progression [177]. This excess risk associated with obesity may be reversible by achieving sustained weight loss through diet or bariatric surgery in the general population [178–180]. However, clear evidence on the harms and benefits of avoiding excessive caloric intake and reducing weight in obese people with ND-CKD is still lacking.

Nonrandomized evidence in obese patients with CKD has suggested that weight loss may lead to better BP control and reduction of the obesity-related glomerular hyperfiltration and proteinuria [180, 181]. Similar data were shown in two RCTs assessing the effect of hypocaloric diet in 17 obese patients and 30 overweight patients, respectively, with proteinuric nephropathies [182, 183]. Meta-analysis of both RCTs showed a significant overall reduction in urinary protein excretion of −1.65 g/24 h (95% CI −3.21 to −0.08), whereas eGFR remained stable during follow-up [8].

In summary, although there is limited evidence of the potential reversibility of the harmful hemodynamic effects, proteinuria, and progression of kidney disease related to obesity, weight reduction through diet and lifestyle modifications could be considered as a component of the therapeutic regimen of obese patients with ND-CKD [177].

Fiber Intake and Probiotics

Evidence is emerging for the effects of fiber intake on CKD progression and mortality in CKD stages 3–5, although only a few small interventional uncontrolled studies have addressed the effects of fiber intake in renal outcomes. In a single-blind crossover study of 13 ND-CKD patients with an eGFR less than 50 ml/min/1.73 m^2, supplementing the diet with fiber significantly reduced p-cresol levels and improved stool frequency [184]. In another uncontrolled trial, the addition of 23 g/day of fiber incorporated into the usual diets of 13 ND-CKD patients was associated with a significant reduction in blood urea nitrogen and creatinine levels, increasing the eGFR from 29.6 ± 3.5 to 32.5 ± 3.6 ml/min/1.73 m^2 after 4 weeks of fiber intervention [78]. These studies suggest with very-low-quality evidence that consuming a highly fermentable fiber, such as inulin, might reduce uremic toxins generation, potentially through the inhibition of proteolytic and enhancement of saccharolytic microbiome.

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Supporting this is a placebo-controlled RCT involving 30 patients with CKD stages 3–4 where total plasma p-cresol concentration was reduced by 40% after taking a synbiotic for 4 weeks [185]. It remains uncertain if increasing fiber intake to normalize intestinal microflora could delay CKD progression to ESRD; even probiotics supplementation has not shown evidence of reducing CKD progression, according to a recent meta-analysis involving eight studies of 261 patients with CKD stages 3–5D (summarized in Table 37.7). However, this therapy may reduce the levels of p-cresol sulfate and elevate the levels of IL-6, thereby protecting the intestinal epithelial barrier of patients with CKD [9].

Dietary Patterns and CKD Progression

Although nutritional management in patients with CKD has been focused on limiting or supplementing the amounts of specific nutrients, epidemiologic and observational evidence suggests that overall dietary pattern might be more protective against CKD progression than excess or deficiency of an isolated nutrient [186–188]. Whereas the so-called Western diet (a high saturated fat diet, rich in red and processed meat and sweets) has been associated with increased risk of CKD progression and albuminuria [186], the Mediterranean diet has been linked to slower kidney function decline and favorable effects on cardiovascular morbidity and mortality [187]. In kidney transplant recipients, the Dietary Approach to Stop Hypertension (DASH) diet has been associated with lower risk of both kidney function decline and all-cause mortality [188]. A lower load and bioavailability of phosphorus (vegetable protein), reduction of the burden of uremic toxins and salt, better control of BP and other cardiovascular risk factors, and reduction of oxidative stress and inflammation are putative mechanisms which could explain the benefits derived from the Mediterranean diet [47]. However, in a systematic review of seven cohort studies involving 15 282 patients, six studies did not show an independent association between healthy dietary patterns (defined as generally consistent with higher intake of fruits and vegetables, fish, legumes, cereals, whole grains, and fiber, and lower in red meat, salt, and refined sugars) and risk of ESRD [155].

There is very limited evidence from interventional studies that adherence to healthy dietary patterns might have effects on CKD progression. In one RCT, 40 ND-CKD patients were randomly assigned to nutritional advice adapted from a Mediterranean diet or to standard care. After 3 months of follow-up, eGFR and creatinine and urea levels remained unchanged in both groups, although it may be argued that the intervention time was too short to assess CKD progression [189]. Conversely, another RCT involving 108 patients with CKD stage 3 followed for 3 years showed a slower progression of kidney disease in the group of patients allocated to dietary alkali treatment with base-producing fruits and vegetables or bicarbonate versus usual care [190].

In summary, it is uncertain whether healthy dietary patterns (independent of other healthy lifestyles) make any difference in preventing the development of ESRD among patients with CKD, although long-term RCTs are warranted [1].

Treatment of PEW in CKD

Prevention and early detection of PEW seems to be essential for the optimal treatment of the syndrome [48, 166, 191]. Important to the prevention of PEW is periodic screening for malnutrition, which must be performed at each patient visit to the clinic or hospital. Through an adequate patient interview, a guided physical examination, and a basic biochemical analysis that includes blood levels of albumin, urea, creatinine, and CRP, the suspected presence of PEW may be determined and a more detailed assessment of the nutritional status should follow, as well as early referral to the dietitian. Symptoms and warning signs include loss of appetite, changes in bowel habits, the appearance of edema, or involuntary weight loss. The routine determination of albumin and CRP allows objective monitoring of the visceral protein deposits and the inflammatory state of patients. Through the urea clearance (otherwise needed for controlling the dialysis dose in patients on dialysis), changes in protein intake can be quantified. In each clinical review, other preventive measures to preserve the nutritional status should be reinforced, including control of the dialysis dose and metabolic acidosis, continuous nutritional counseling, and supportive messaging about the benefits of adequate physical exercise tailored to each patient [48]. Table 37.8 shows a protocol used to monitor nutritional status and treat PEW in CKD patients.

With a frequency that usually ranges between 4 weeks and 4 months, depending on the CKD stage (the more advanced the stage, the more frequent the nutritional assessment), and whenever PEW is suspected in CKD patients, a more detailed assessment of nutritional status should be conducted. Recommendations for this assessment include an SGA score to provide a more detailed collection of the signs and symptoms of malnutrition, the determination of prealbumin and transferrin levels, which can reflect changes in nutritional status earlier than albumin, performance of bioimpedance if available (otherwise, the determination of the mid-arm circumference as a marker of muscle mass), and measurement of muscle strength by hand dynamometry.

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Table 37.7 Summary of findings: probiotics supplementation for adults with CKD.

Outcomes	No. of participants (no. of studies)	Absolute number of patients affected per 1000 patients treated for one year (95% CI)	Relative effect (95% CI)[a]	Certainty of the evidence (GRADE)	Conclusion
Serum creatinine	250 (5)	Not estimable	The MD for serum creatinine was 0.08 mg/dl higher (0.13 lower to 0.28 higher) with probiotics compared to placebo	Very low ●○○○	It is uncertain whether probiotics supplementation impacts on serum creatinine levels compared to placebo
Blood urea	164 (3)	Not estimable	The MD for blood urea was 1.38 mg/dl lower (9.26 lower to 6.15 higher) with probiotics compared to placebo	Very low ●○○○	It is uncertain whether probiotics supplementation impacts on blood urea levels compared to placebo
p-cresol sulfate	125 (3)	Not estimable	The SMD for p-cresyl sulfate was 0.57 lower (0.99 lower to 0.14 lower) with probiotics compared to placebo	Low ●●○○	Probiotics may slightly reduce p-cresyl sulfate levels of CKD patients compared to placebo
Hemoglobin	93 (3)	Not estimable	The MD for hemoglobin was 0.21 g/dl higher (0.48 lower to 0.91 higher) with probiotics compared to placebo	Low ●●○○	Probiotics may slightly improve hemoglobin levels of CKD patients compared to placebo
Interleukin-6	134 (3)	Not estimable	The SMD for interleukin-6 was 0.37 higher (0.03 higher to 0.72 higher) with probiotics compared to placebo	Very low ●○○○	It is uncertain whether probiotics supplementation impacts on interleukin-6 levels compared to placebo
C-reactive protein	106 (3)	Not estimable	The MD for C-reactive protein was 0.64 mg/dl higher (3.81 lower to 5.09 higher) with probiotics compared to placebo	Very low ●○○○	It is uncertain whether probiotics supplementation impacts on C-reactive protein levels compared to placebo

CKD, chronic kidney disease.
Treatment estimates are drawn from a Cochrane review [9]. GRADE assessment of the certainty of the evidence [17]: High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different* is low. Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different* is moderate. Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different* is high. Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different* is very high. *Substantially different = a large enough difference that it might affect decision-making.
[a] Effects are reported as mean difference (MD) and 95% confidence interval (CI) for continuous outcomes (standardized mean difference [SMD] if different scales were used).
Source: Jia L, Jia Q, Yang J, Jia R, Zhang H. (2018); Hultcrantz M, Rind D, Akl EA, Treweek S, Mustafa RA, Iorio A, et al. (2017).

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Table 37.8 Suggested strategies for early detection and treatment of PEW in CKD patients.

	Warning signs	Potential interventions
Periodic nutritional screening (in each clinical visit)		
Actual body weight and ideal weight	Unintentional weight loss >5% of ideal body weight or estimated dry weight or weight <85% of ideal weight	If PEW is suspected, a more detailed nutritional assessment and an early referral to the renal dietitian are mandatory
Dietary intake	Loss of appetite	Other preventive measures: 1) Dietary assessments to evaluate whether the intake provided with the diet is adequate in protein and caloric contents 2) Correction of metabolic acidosis 3) Achievement of adequate dialysis dose 4) Good oral hygiene 5) Treatment of digestive symptoms as needed (nausea/vomiting) 6) Adequate physical exercise (as tolerated) 7) Management of comorbidities (diabetes, chronic heart failure, etc.) 8) In-center meals (dialysis)
Serum albumin	<3.8 g/dl	
C-reactive protein	>10 mg/dl	
Urea clearance to estimate the protein intake (and calculate the dialysis dose)	<1.2 g/kg/day in dialysis <0.6 g/kg/day in nondialysis dependent CKD	
Creatinine levels to calculate the creatinine index in dialysis patients[a]	<20 g/kg/day or significant reduction	
Detailed assessment (at least two to four times/year or whenever PEW is suspected)		
Subjective global assessment	Score of B or C	• An etiopathogenic approach: 1) Treatment of inflammatory causes: intercurrent infections, nonfunctioning renal graft, use of central venous catheters 2) Uremic symptoms: optimize dialysis if needed 3) Pill burden reduction (i.e. phosphate binders): consider dose reduction or temporary discontinuation of treatment 4) Treatment for gastroparesis in diabetic patients • Dietary counseling • Oral nutritional supplements • Tube feeding or percutaneous endoscopic gastrostomy • Intradialysis parenteral nutrition (for hemodialysis patients) • Intraperitoneal nutrition (for peritoneal dialysis patients) • Total parenteral nutrition • Adjunct therapies: appetite stimulants; anabolic hormones (androgens, growth hormone); anti-inflammatory interventions (omega-3)
Prealbumin	<30 mg/dl or significative reduction	
Transferrin	<200 mg/dl or significative reduction	
Mid-arm circumference	Significative reduction	
Bioelectrical impedance	Loss of muscle mass or fat mass	
Hand dynamometry	Loss of strength	
Dietary intake assessment	Protein intake <1.2 g/kg/day in dialysis or <0.6 g/kg/day in nondialysis dependent CKD Energy intake <30–35 kcal/day	

CKD, chronic kidney disease; PEW, protein-energy wasting.

[a]The equation to estimate creatinine index (CI) was developed based on age, gender, predialysis serum creatinine concentrations, and spKt/V urea with the simplified equation from Cannaud et al. [135] [$16.21 + 1.12 \times (1\ si\ man; 0\ si\ female) - 0.06 \times \text{age (years)} - 0.08 \times \text{sp}Kt/V + 0.009 \times \text{Cr}_{pre}(\mu\text{mol/l})$]. To evaluate CI using plasma creatinine concentration in mg/dl, divide the creatinine concentration term by 88.4.

Source: Adapted 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 Dec;84(6):1096–107.

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Dietary Counseling

In patients for whom preventive approaches to PEW have been insufficient, the first therapeutic step should be intervention by a nutritionist, who will carry out a dietary assessment to evaluate whether the dietary intake is adequate in protein and caloric contents. This intervention may support initiating therapy with oral nutritional supplements (ONS) [48].

The randomized evidence to determine whether providing individual nutrition counseling improves nutritional status in ND-CKD patients is limited to one RCT involving 56 patients with CKD stages 4–5 [192, 193]. Patients were randomly allocated to fortnightly, individualized counseling on a prescription of 0.75 g/kg/day of protein and 145 kJ/kg/day of energy versus written education material for 3 months. During the 12-week follow-up, the intervention group had less decrease in body cell mass, greater increase in energy intake, and greater improvement in SGA score compared with the control group.

Two RCTs have demonstrated dietary counseling may improve several nutritional parameters for patients with CKD stage 5D [194, 195]. In the largest trial to date, 180 HD patients with baseline albumin levels less than 3.7 g/dl were randomized to identify and intervene on specific modifiable nutritional barriers (i.e. low nutritional knowledge, decreased appetite, or gastrointestinal symptoms) versus usual care; results showed significant improvements in protein and energy intakes and albumin levels regardless of levels of inflammatory markers [193]. According to another, small RCT, intensive nutritional counseling might be of greater benefit than nutritional supplements alone in the management of PEW in HD patients [195].

Oral Nutritional Supplements

ONS can offer an additional source of protein (0.3–0.4 g/kg/day) and energy (7–10 kcal/kg/day) for achieving the recommended targets (Table 37.2) in CKD patients with a decreased spontaneous nutrient intake. ONS are usually recommended to be administered two or three times a day, always after meals ("as a dessert") to avoid losing appetite, or during the HD session [39]. The nutritional response to therapy is directly correlated with severity of PEW at baseline [48].

The efficacy of oral supplements to improve nutritional status in dialysis patients has been tested in a number of small RCTs, which have been meta-analyzed in a recent systematic review of 15 studies with 589 subjects (Table 37.9) [10]. Compared with placebo or routine care, provisions of ONS resulted in a significant increase in BMI and albumin levels, with no effects on phosphorus or potassium levels. Evidence for beneficial effects of ONS is restricted to effects on nutritional parameters, as RCTs did not have sufficient statistical power to allow meta-analysis of patient-centered outcomes, such as survival, quality of life, or cardiovascular events. Given the short follow-up and the small sample sizes of the studies, the quality of the evidence according to the meta-analysis was considered very low.

Only one RCT has assessed the effects of protein supplementation on mortality in the dialysis population as a primary endpoint [196]. However, it compared only oral protein supplement with intradialytic parenteral nutrition (IDPN) and did not include a usual care arm, probably because of the ethical implications of withholding nutritional therapy to malnourished patients. Body weight, serum albumin, and PNA increased in both groups. Similarly, there were no differences between the two groups regarding mortality.

The randomized evidence for ONS in PD patients is very limited and shows a higher rate of noncompliance and intolerance compared to HD patients [39, 197]. In an open-label RCT, 28 PD patients were allocated to an oral egg albumin-based supplement versus conventional nutritional counseling. During a 6-month follow-up, the treatment group had significantly improved serum albumin, calorie and protein intake, and nPNA [198]. In a 4-month RCT involving 100 PD patients with malnutrition, calcium caseinate versus usual care resulted in a significant increase in serum albumin levels [199]. Evidence for ONS in renal transplant and ND-CKD patients is absent, although ONS might help to prevent PEW in patients on LPD [200].

Altogether, very-low-quality evidence suggests that short-term oral energy or protein/amino acid supplements may improve nutritional status in dialysis patients, without influence on serum phosphorus or potassium levels.

In those patients with oral intolerance to ONS, nasogastric tubes, percutaneous endoscopic gastrostomy, or jejunostomy probes can be used. These nutritional treatments are usually reserved for patients with severe, postsurgical, critical anorexia or with problems swallowing due to neurological alterations or head and neck surgery. Randomized evidence for enteral tube feeding in the CKD population is absent [201].

Intradialytic Parenteral Nutrition in HD

Although the enteral route is the initial treatment of choice for nutritional supplementation, parenteral provision of nutrients during the HD session can be considered for patients who continue to be malnourished despite ONS or who are unable to tolerate oral supplementation (e.g. those with severe gastroparesis). Although the optimal duration of treatment is unknown, a trial of 3–6 months is recommended to assess the response to IDPN. IDPN is usually

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Table 37.9 Summary of findings: oral nutritional supplements for adults with CKD on dialysis.

Outcomes	No. of participants (no. of studies)	Absolute number of patients affected per 1000 patients treated for one year (95% CI)	Relative effect (95% CI)[a]	Certainty of the evidence (GRADE)	Conclusion
Primary outcomes					
Death (all causes)	— (–)	—	No studies	Absent	No studies were found that evaluated the impact of ONS on survival
Cardiovascular events	— (–)	—	No studies	Absent	No studies were found that evaluated the impact of ONS on the appearance of cardiovascular events
Infectious events	— (–)	—	No studies	Absent	No studies were found that evaluated the impact of ONS on the appearance of infectious events
Health-related quality of life	— (–)	—	No studies	Absent	No studies were found that evaluated the impact of ONS on health-related quality of life
Secondary outcomes					
Body mass index	376 (9)	Not estimable	The MD for the effect of BMI was 0.40 kg/m^2 higher (0.10 higher to 0.71 higher) with ONS compared to control or standard care	Low ●●○○	ONS may increase body mass index
Serum albumin	507 (14)	Not estimable	The MD for the effect of serum albumin levels was 1.58 mg/dl higher (0.52 higher to 2.63 higher) with ONS compared to control or standard care	Moderate ●●●○	ONS probably increases serum albumin levels

BMI, body mass index; CKD, chronic kidney disease; ONS, oral nutritional supplements.
Treatment estimates are drawn from a Cochrane review [10]. GRADE assessment of the certainty of the evidence: [17] High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different* is low. Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different* is moderate. Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different* is high. Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different* is very high. *Substantially different = a large enough difference that it might affect decision-making.
[a] Effects are reported as the relative risk (RR) and 95% confidence interval (CI) for binary outcomes and mean difference (MD) and 95% CI for continuous outcomes (standardized mean difference [SMD] if different scales were used).
Source: Liu PJ, Ma F, Wang QY, He SL. (2018); Hultcrantz M, Rind D, Akl EA, Treweek S, Mustafa RA, Iorio A, et al.(2017).

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administered only 3 days per week for 4 hours, thus it is not appropriate for severely malnourished patients, in whom total parenteral nutrition may be necessary to provide sufficient proteins and calories to treat PEW [48].

A 2010 systematic review of RCTs compared IDPN with usual diet, placebo, or ONS; it included three studies with 220 HD patients [202]. Unfortunately, there were insufficient data to undertake a meta-analysis of whether IDPN improves survival, quality of life, or nutritional status. In the largest trial in the review (and to date), 186 malnourished HD patients received ONS with or without 1 year of IDPN [196]. The study showed an improvement in nutritional markers in both groups, indicating that the addition of IDPN to ONS did not provide additional benefit over ONS alone; no differences in survival were noted. A 2017 RCT compared IDPN given three times weekly versus dietary counseling in 107 HD patients with PEW. IDPN for 16 weeks resulted in a significant increase in mean serum prealbumin, although without changes in SGA score or quality of life [203].

The conclusion then is that although IDPN might be used in highly selected patients with positive results, it is uncertain whether IDPN improves quality of life, decreases mortality, or prevents hospitalizations. This is in agreement with the results of a recently published systematic review that included both interventional and observational studies [11].

Intraperitoneal Infusion of Amino Acids in PD

Although use of amino acids in the dialysate may be an adequate nutritional intervention for malnourished PD patients who are unable to tolerate ONS, evidence in this regard is limited to one small RCT [204]. Improvements in overall protein balance (protein synthesis minus protein breakdown) was observed with the use of a dialysate that contained amino acids and glucose versus glucose as control dialysate in a crossover study of eight patients over 14 days. Whether this dialysis procedure may improve the nutritional status in malnourished PD patients remains uncertain.

Non-nutritional Interventions for PEW

In addition to correcting any nutritional deficiencies, treatment of malnourished CKD patients should always include an ethological approach to identify the causes involved in PEW [48]. Inflammation may be a cause of anorexia and increased energy expenditure, which increases the risk of developing PEW. This inflammation can be caused by a wide range of potentially treatable factors (Box 37.1). Although periodic determination of CRP to help assess the presence of underlying and treatable inflammatory processes would be beneficial [43, 48], this recommendation is based on epidemiological evidence linking inflammation to poor outcome in the CKD population [130]; there are no RCTs to suggest that outcomes are improved by nonspecific inflammation-reducing modalities.

The treatment of the different comorbidities could also help to correct PEW (i.e. adequate metabolic control for diabetes or antidepressants for mood disorders). Although the quality of evidence for the ethological approach to PEW is very low or absent, a few small randomized and quasi-randomized controlled trials have shown the benefits of increasing both solute diffusion and convection on the nutritional status of dialysis patients [88, 89]. Thus, improving dialysis adequacy, with interventions aimed at enhancing solute clearance, might impact positively on PEW, although quality evidence is lacking [48].

Other additional therapeutic measures to correct PEW, most of them considered as experimental, may include the use of appetite stimulants such as megestrol acetate, anti-inflammatory drugs, and exercise and anabolic agents [48].

Megestrol Acetate

Evidence for the use of megestrol acetate as orexigenic is restricted to dialysis patients. A systematic review of three RCTs and six observational studies assessing the efficacy and safety of megestrol acetate was published in 2016 [12].

Box 37.1 Nonspecific Inflammation-reducing Interventions for Protein-energy Wasting in Patients with Chronic Kidney Disease

Screen and treat occult infections:
- Urinary tract infections
- Diabetic foot ulcers
- Gut flora dysbiosis
- Tuberculosis

Assess for poor dental hygiene and periodontal disease

Routinely assess for volume overload

Screen and treat rheumatologic conditions:
- Vasculitis
- Systemic lupus relapses
- Rheumatoid arthritis

Screen for pericarditis

Embolize or remove nonfunctioning renal allografts

Optimize vascular access
- Replace central venous catheters with arteriovenous fistula
- Remove nonfunctioning arteriovenous grafts

Optimize hemodialysis prescription
- Replace standard dialysate fluid with ultrapure dialysate
- Replace bioincompatible membranes with biocompatible membranes
- Replace standard hemodialysis with on-line hemodiafiltration

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All three RCTs were limited by small sample sizes (range 9–22 subjects), short duration (range 8–24 weeks), a high degree of bias, and absence of clinical outcomes such as quality of life or hospitalizations. Appetite, serum albumin, and body weight significantly increased in some but not all the studies. Altogether, it is uncertain whether megestrol acetate impacts on PEW. In addition, use of megestrol acetate was associated with significant adverse events, which were especially noted in the six observational studies, and there were no data regarding the safety of using megestrol acetate beyond 24 weeks [12].

Anti-inflammatory Agents

In addition to treating inflammation directly due to a specific identified source (e.g. an ongoing chronic infection), the use of anti-inflammatory agents in malnourished CKD patients has been tested in several RCTs. A meta-analysis of RCTs assessing the anti-inflammatory effects of fish oil containing omega-3 polyunsaturated fatty acids versus placebo or no treatment was published in 2016 [13]. It involved 13 studies with 916 patients with CKD stage 5D on HD, and showed that fish oil significantly reduced some CRP and high-sensitivity CRP but not all inflammatory markers. In addition, fish oil reduced the risk of arteriovenous (AV)-graft events and cardiovascular events and alleviated depression symptoms, although no effect on albumin levels was noted. In 2014, two meta-analyses examined the effects of L-carnitine supplementation in HD patients, with mixed results [14, 15]. Whereas in one meta-analysis (49 RCTs, 1734 participants) there was a significant decrease in CRP levels noted [14], the other review (25 studies, 1172 participants) indicated this therapy did not result in a significant reduction in CRP levels [15]. In a small uncontrolled trial, daily supplementation with Brazil nut (the richest known food source of selenium) for 3 months resulted in a significant decrease in cytokines and other inflammatory and oxidative markers [205].

Besides the anti-inflammatory effects related to some nutrient supplementation, some drugs may also exert the same effects in CKD populations. In 2012, a meta-analysis summarized the evidence for the effect of statin therapy on inflammatory and nutritional markers in dialysis patients. Nine RCTs involving 3098 patients were analyzed, with the resulting report of a significant decrease in CRP and high-sensitivity CRP levels but no effect on serum albumin levels [16]. In a small RCT of 108 HD patients, sevelamer hydrochloride versus calcium acetate lowered high-sensitivity CRP after a 1-year follow-up [206]. An uncontrolled trial of 24 HD patients noted a reduction in CRP and IL-6 after a 3-month intervention with *N*-acetylcysteine [207]. Pentoxifylline, anti-TNF agents, and recombinant IL-1 receptor antagonists have also been tested in the treatment of inflammation in patients with CKD.

Anabolic Agents

Anabolic agents including recombinant human GH and androgenic steroids may also be effective in CKD patients with PEW. In a 4-week follow-up RCT involving 17 malnourished dialysis patients, treatment with recombinant human GH, whose use is approved for pediatric patients with CKD and short stature, significantly increased weight gain and IGF-1 and transferrin levels, suggesting that short-term GH administration might be associated with an anabolic reaction in malnourished dialysis patients [208]. However, the long-term nutritional benefits of GH have been not demonstrated [209]. In an RCT involving 29 patients undergoing dialysis, treatment with nandrolone versus placebo for 6 months resulted in a significant increase in lean body mass associated with functional improvement, including a decrease in the time to complete the walking and stair-climbing test [210]. Despite this positive effect on protein stores, the long-term efficacy and risk for adverse effects of androgenic anabolic steroids remains unclear, thus limiting their role in medical practice.

Overall, evidence on the safety and effectiveness of anti-inflammatory drugs and anabolic agents in CKD patients is very low, hindered by small studies, with limited follow-up, and focused primarily on HD patients. Large-scale RCTs are needed to confirm these anti-inflammatory effects.

Lastly, although an aerobic and resistance exercise program in well-nourished CKD patients may improve physical capacity and quality of life [211], no data are available regarding the anabolic effect of exercise in CKD patients with PEW.

Conclusions

Attention to nutritional status is critical as it may impact on important clinical outcomes in patients with CKD, including CKD progression, quality of life, morbidity, and mortality. Although some interventional studies have shown that nutritional interventions may have reno-protective effects and improve surrogate markers of survival, high-quality evidence is still insufficient. However, this lack of evidence does not necessarily indicate that nutritional interventions have no effect on CKD outcomes. Given that nutritional therapy, including dietary counseling and supplements, is safe and cost-effective, it should be considered to improve the poor prognosis of CKD patients.

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Preparation for Dialysis

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Introduction

Chronic kidney disease (CKD) is a progressive disorder associated with increased morbidity, cost of treatment, and mortality. When identified early, CKD progression to end-stage kidney disease (ESKD) can be delayed or halted. However, once CKD has significantly advanced (estimated glomerular filtration rate [eGFR] <30 ml/min/1.73 m^2), very little can be done to sufficiently delay progression of disease to avoid the need for renal replacement therapy (RRT) [1]. The number of people with advanced CKD is high globally. For instance, the United States Renal Data System (USRDS) 2018 annual report showed that the overall prevalence of CKD (stages 1–5) in the United States adult general population was 14.8% in 2013–2016 (CKD stage 3 was the most prevalent [6.4%]) [2]. Although RRT is often inaccessible to many across the world [3], in places where treatment is available it is important that patients are adequately prepared for treatment initiation. In many instances, however, patients with CKD will not be prepared for RRT, especially in developing countries where patients are often "crash-landers" requiring RRT at time of first contact with nephrologist [4, 5]. Preparation for dialysis, when carried out through a multidisciplinary process, has been shown to be associated with better patient survival [6] or slower decline in glomerular filtration rate (GFR) compared to patients receiving usual care [7]. Strategies for retarding progression of CKD and treating complications associated with CKD are discussed in detail in Chapters 31 to 37. This chapter focuses on the approach to dialysis modality selection, patient education, and preparation for specific modalities.

Epidemiology of ESKD and Dialysis Therapies

It is widely known and accepted that ESKD is a noncommunicable disease with global impact and public health importance. ESKD represents the final phase in the spectrum of CKD and is typified by the occurrence of worsened biochemical and metabolic profiles. Although a greater percentage of CKD patients are likely to die from cardiovascular-related causes rather than progress to ESKD [8, 9], those who do progress usually need the introduction of RRT, such as dialysis, for survival.

There has been a steep increase in the prevalence of ESKD since the first forms of RRT were instituted about six decades ago. In the United States, an increasing prevalence of ESKD continues to be observed despite plateauing incidence rates; a recent summary of the United States Renal Data System (USRDS) reports a yearly increase of about 21 000 ESKD prevalent cases per year [10]. A similar pattern of increase has been observed in Europe [11]. This epidemiologic trend has far-reaching implications with regards to the initiation and provision of RRT due to increasing need and resource implications. The global prevalence of ESKD is presently estimated at 0.1%, with known notable inter- and intra-regional differences in the availability and access to RRT. There will be a continued increase in the incidence and prevalence of ESKD and dialysis therapies due to increasing age, the increasing burden of chronic diseases such as diabetes mellitus and hypertension, as well as advances in the treatment of these diseases

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which promote longevity. In addition, the contribution of chronic infectious disease-related ESKD, such as HIV-associated nephropathy and hepatitis B- and C- associated kidney disease, to this burden cannot be overlooked.

Maintenance dialysis modalities have become the more predominant forms of RRT; kidney transplantation remains an underutilized RRT option due to reasons such as organ scarcity and the unbearably high costs of setting up and running renal transplant programs, especially for many developing nations [12]. There were approximately 284 patients per million population (pmp) receiving maintenance dialysis in 2010 [13]. Incidence rates (i.e. initiation rates) of maintenance dialysis have been the highest in low- to middle-income countries due to improved access to dialysis therapies. Prevalence rates are on the increase globally; rates have increased, albeit disproportionately, by between 154% and 170%. Prevalence rates have been estimated at >2000 patients pmp, 750–1999 patients pmp, 10–99 patients pmp, and <0.1 patients pmp in North America, Europe (excluding Russia), Central Asia, and West Africa, respectively [13].

Timing of Nephrology Referral (Early vs. Late) and Outcomes

Although there is no consensus on the ideal timing for nephrology referral of the CKD patient, most societal/organizational guidelines recommend that CKD patients should be referred to a nephrologist when GFR is <30 ml/min/1.73 m^2 (i.e. stage 4). Early referral ensures that the choice of care (conservative or active, peritoneal dialysis [PD] or hemodialysis [HD]) can be a shared decision-making process rather than an option chosen out of dire necessity [14]. It also ensures that the discussion about ESKD care with respect to RRT options such as renal transplantation and the various alternatives of HD and PD therapies can be established. It has been demonstrated that the timing of nephrology referral influences the eventual dialysis modality selected and the creation of the required vascular access in the circumstances of hemodialytic therapies [15]. Early referral of the CKD patient to the nephrologist provides ample time for permanent access creation and the opportunity to address any complications that might occur before dialysis becomes needed (Table 38.1).

Table 38.1 Consequences of late referral and benefits of early referral of CKD patients to nephrologist.

Consequences of late referral[a] of patients with CKD	Benefits of early referral[b] of patients with CKD
• Inadequate control of diabetes, blood pressure, hyperlipidaemia, and malnutrition	• Prevention and management of modifiable risk factors of CKD
• Inadequate management of anemia and mineral bone disease	• Optimization of treatment of CKD
• Rapid deterioration of renal function	• Delayed progression of CKD
• Increased hospitalizations and duration of in-hospital stay	• Access to structured educational programs
• Increased cardiovascular morbidity and mortality	• Adaptation of CKD patient to RRT treatment
• Poor preparation for dialysis	• Preparation and creation of suitable dialysis access
• Inadequate psychological preparation and support	• Avoidance or lesser need for temporary vascular access
• Loss of opportunity to participate in shared decision-making on dialysis modality and initiation	• Training on selected modality of RRT
• Less chance of initiating RRT with PD	• Better compliance
• Increased chance of use of temporary access with associated complications	• Increased opportunity for pre-emptive kidney transplantation
• Increased need for urgent start of dialysis	• Reduction of cardiovascular morbidity and mortality
• Increased chance of poor compliance to treatment due to poor understanding	• Reduction of management costs due to better planning
• Lack of pre-transplant evaluation and loss of opportunity for pre-emptive kidney transplant	
• Excessive management costs	

CKD, chronic kidney disease; RRT, renal replacement therapy; PD, peritoneal dialysis.
[a] Referral of patients with CKD <3 months before initiation of dialysis.
[b] Primary healthcare physician should ideally refer patients with CKD at stage 1 if hematuria or significant proteinuria is present, at stage 2 if eGFR declines >4 ml/min/year, and at stage 3 for all patients with CKD where eGFR is <60 ml/min/1.73 m^2.
Source: Adapted from Karkar [14]. © 2011, Wolters Kluwer.

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Importance of Patient Educational and Learning Programs

Management of patients with CKD can be complicated given that at early stages CKD is usually an asymptomatic condition. Explaining this diagnosis to a patient, who is expected to make major lifestyle changes, can pose significant challenges in the face of low public awareness of kidney diseases in general [16, 17]. Several studies have shown that awareness of kidney disease is low amongst patients. Tuot et al., using 1999–2008 National Health and Nutrition Examination Survey (NHANES) data in 1852 adults with eGFR <60 ml/min/1.73 m^2, assessed whether markers of kidney disease that should trigger CKD recognition among providers are associated with higher individual CKD awareness [18]. They reported that 90% of individuals with two to four markers of CKD and 84% of individuals with five or more markers of CKD were unaware of having CKD. Only those with albuminuria had greater odds of CKD awareness than those without (adjusted odds ratio 4.0, $P < 0.01$) [18].

Patient education is a process and should begin from the time when the physician reveals the diagnosis, which should be delivered at the patient's pace of understanding with empathy and conveyance of hope [19]. This initial message should be given in a quiet place that is free of interruptions, and preferably when the patient is accompanied by supportive family or friend or in the presence of supportive staff or care giver (e.g. nurse, counsellor, or social worker) [19, 20]. Potential dialysis patients need information not only about the mechanics of specific dialysis modalities but also the associated features of such therapy to help make informed choices. Predialysis CKD education should be individualized according to available resources and the level of knowledge of the patient, and should include tours of dialysis facilities, meeting patients who are undergoing treatment with different dialysis modalities, use of videos and written materials, and behavior-changing protocols with small-group problem-solving activities [21]. Other education program contents could include discussion of CKD risk factors, interpretation of kidney function tests, complications of CKD, interventions to slow loss of kidney function, dietary changes necessitated by disease state, different options for dialysis and their impact on the individual's lifestyle, travel and time commitments for in-center HD treatment, importance of preserving upper extremity veins for future dialysis access, timing of placement of dialysis access, renal transplantation, and financial costs and insurance coverage [22].

There is evidence that educational interventions can be a useful tool for improving knowledge on various aspects of CKD (including risk factors), patient self-management, and patient outcomes [23–26]. Lopez-Vargas et al. [27] in a systematic review of educational interventions in CKD patients that included 26 studies (12 trials, 14 observational studies involving 5403 participants) broadly categorized the primary outcomes of educational interventions into two groups: (i) patient-reported outcomes (e.g. quality of life, psychosocial function, knowledge, self-management, and lifestyle modification) [28–32] and (ii) clinical end points (eGFR, dialysis therapy commencement, survival, blood pressure, and biochemical markers) [26, 33–36]. They reported that the characteristics of effective interventions included those with interactive and practical skills teaching sessions (13/15 studies), integrated negotiated goal setting (10/13 studies), involved groups of patients (12/14 studies), their families (4/4 studies), and a multidisciplinary team (6/6 studies), and frequent participant/educator encounters (weekly [4/5 studies], monthly [7/7 studies]) [27]. Kurella Tamura et al. [37] evaluated the role of participation in a kidney disease screening and education program in improving ESKD preparation and survival in 595 adults who developed ESKD after participating in the National Kidney Foundation Kidney Early Evaluation Program (KEEP). They identified and selected non-KEEP patients from a national ESKD registry and matched them to KEEP participants based on demographic and clinical characteristics. KEEP participants were more likely to see a nephrologist before ESKD (76.0% vs. 69.3%, $P < 0.01$), more likely to use PD versus HD (10.3% vs. 6.4%, $P < 0.01$), more likely to be placed on the transplant waiting list before ESKD (24.2% vs. 17.1%, $P < 0.01$), and more likely to undergo transplantation (9.7% vs. 6.4%, $P < 0.01$), although they were not more likely to undergo pre-emptive transplantation (1.7% vs. 1.5%, $P = 0.7$). KEEP participants were slightly more likely to use an arteriovenous (AV) fistula or graft (23.4% vs. 20.1%, $P = 0.09$) at the first outpatient dialysis and slightly more likely to have a mature or maturing arteriovenous fistula or graft at the first outpatient dialysis (44.0% vs. 39.6%, $P = 0.06$).

Modality Selection and Timing of Dialysis Initiation

Modality Selection

Counseling CKD patients about RRT options for ESKD is a distinct educational process. Patients in late stage 3 and stage 4 CKD should be educated on a range of potential options, including home and in-center dialysis modalities, transplantation, and in appropriate cases where RRT cannot be offered, conservative care (Figure 38.1) [38]. In the United States, more than 90% of patients initiating RRT commence

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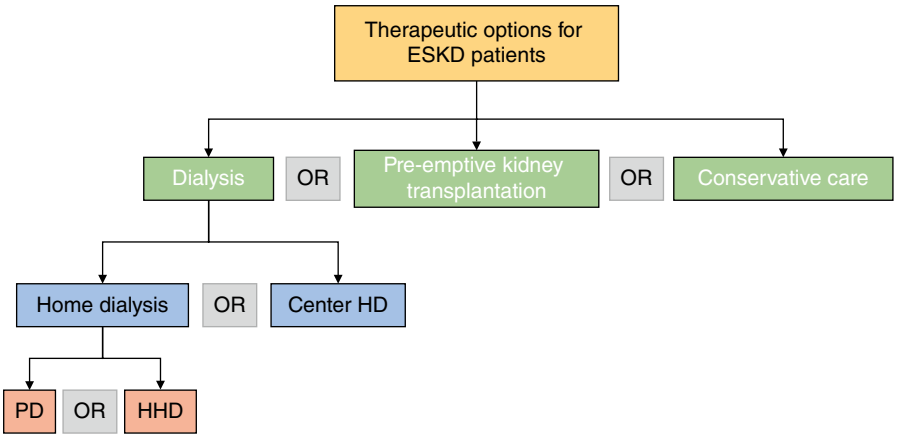

Figure 38.1 Treatment options for patients with end-stage kidney disease. HD, hemodialysis; HHD, home hemodialysis; PD, peritoneal dialysis.

therapy using in-center HD, with approximately 8.5% initiated on PD while the rest receive treatment through other modalities (home HD [<2%], conservative management [<1%], and pre-emptive kidney transplant [<1%]) [39]. There are geographic differences in the modality patients are likely to initiate RRT on depending on government policy and the country's economic status [40, 41]. Other factors like the patient's clinical (comorbid) conditions and the nephrologist's familiarity with each technique also play a role on modality selection; often, however, little attention is given to individual patient preferences [42].

Selecting a dialysis modality is a complex decision process for the patient. Murray et al. have shown that factors influencing a CKD patient's participation in the decision-making included interpersonal relationships; preservation of current well-being, normality, and quality of life, need for control, and personal importance on benefits and risks [43]. Patient involvement in modality selection through shared decision-making is advocated to support patients deciding on a modality of treatment suitable to their clinical condition, lifestyle, and social circumstances [44]. However, for shared decision-making to occur, the patient must be willing to be involved in their dialysis treatment decision. This is not always observed as studies have shown that up to 27% of patients may prefer a passive role in treatment decision-making [45–47]. Also, due to resource constraints, the choice of modality may be made only by physicians (e.g. in South Africa where RRT is rationed) [4]. Barriers to shared decision-making have been explored and include time needed to integrate shared decision-making in clinical practice, patients preference not to be involved in the process of decision-making, and disagreement amongst healthcare professionals on asking patients about their preference (some patients are information receivers and others are engagers) [48–50]. However, the shared decision-making model provides an ideal framework to involve patients in selection of the best treatment option suitable to them [44]. In the Empowering Patients on Choices for Renal Replacement Therapy (EPOCH-RRT) study, a cross-sectional study was designed to assess patients' perspectives at the time they choose a dialysis modality [51]. It included 180 patients with advanced CKD, either nondialysis dependent or on dialysis therapy (HD and PD) across the United States. Maintaining as much independence as possible, quality and quantity of life, and flexibility in daily schedule were the themes most often reported by patients as important for choice of modality. About half of the HD patients (47%) believed that the decision to be treated by HD had largely not been their choice; this was only reported by 3% of PD patients. The study findings supported the need for interventions to improve shared decision-making on dialysis treatment options, targeting both patients and clinicians.

Expected patient survival on dialysis is a major factor that influences choice of treatment modality. Several studies have assessed the relationship between dialysis modality and survival; most studies report an initial survival benefit on PD within the first 2 years of treatment initiation, but a less favorable long-term survival for PD compared with HD [52–54]. In a recent study that used data from 196 076 patients within the European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) Registry who started RRT between 1993 and 2012, van de Luijtgaarden et al. reported a reduction of PD incidence and prevalence with time [55]. They also showed that there was a similar 5-year patient survival for PD versus HD in 1993–1997 (adjusted hazard ratio [HR] 1.02, 95% confidence interval [CI] 0.98–1.06), while patient survival was higher for PD patients in 2003–2007 (HR 0.91, 95% CI 0.88–0.95). Thus, although initiating RRT on PD was associated with favorable patient survival when compared with starting on HD treatment, PD was often not selected as initial dialysis modality.

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Although home hemodialysis (HHD) is becoming an increasingly available RRT option, patient selection criteria may confound comparison with other RRT modalities. For instance, HHD patients in Australia and New Zealand are usually younger and have fewer comorbidities than patients undergoing PD and in-center HD [56, 57]. One study that included 10 710 patients on incident PD and 706 patients on incident HHD reported that treatment with HHD was associated with better patient survival than treatment with PD (5-year survival 85% vs. 44%, respectively, log-rank $P < 0.001$) [57]. Another study showed that home dialysis (home HD + PD) had a 13% lower mortality risk compared to facility HD, while PD showed a 20% lower mortality risk in the early period (<3 years) that is offset by a 33% greater mortality risk in the late period (>3 years), with no overall net effect [56]. When the attributes of dialysis care and the trade-offs that patients considered when making decisions about dialysis modalities was quantified, Walker et al. reported that patients preferred home dialysis over facility-based care when increased nursing support was available and when longer survival, wellbeing, and flexibility were expected. In addition, they showed that sociodemographic factors (age, ethnicity, and income) also influenced patients' choices [58].

Given that the presence of some comorbidities or patient features may be a relative or absolute contraindication to the desired dialysis modality (Table 38.2) [59], patients should be informed about this and guided toward other options. Patients should also understand that no care plan is completely inflexible, and modality switching can and should occur if an initial choice is deemed less than optimal by the patient and kidney care team.

Table 38.2 Contraindications to specific dialysis modalities.

Hemodialysis	
	Relative contraindications • Difficult vascular access – Severe peripheral arterial vascular disease – Central vein stenoses or occlusions • Desired home dialysis with lack of appropriate home environment or partner
Peritoneal dialysis	
	Absolute contraindications • Extensive abdominal adhesions • Hydrothorax or diaphragmatic defects • Loss of peritoneal membrane function (ultrafiltration, solute clearance) Relative contraindications • Morbid obesity • Severe protein calorie malnutrition • Loss of residual renal function • Bowel disease – Ischemic – Chronic inflammatory – Diverticulosis or diverticulitis

Source: Adapted from Parker and Himmelfarb [59].

Timing of Dialysis Initiation

The optimal time to initiate maintenance dialysis is currently unknown; many patients are vulnerable during this transition period as it has been reported that the majority of patients are unprepared and ill-informed about commencing dialysis [42]. The factors surrounding timing of initiation of treatment are often multifaceted and are often different for patients and care providers. For instance, one study reported that patients based their choice on a "gut instinct," as well as the effects of commencing treatment on quality of life and survival, while care providers considered biomedical factors and an instinct to prolong life [60]. In the United States, provider characteristics such as graduating from a nondomestic medical school and greater experience (length of time of practice) have been linked with timing of initiation of treatment [61]. Various guidelines published after the Initiating Dialysis Early and Late (IDEAL) study [62] have generally recommended a late commencement of dialysis (eGFR <6–10 ml/min/1.73 m^2) and, importantly, for dialysis initiation to be guided by the patient's clinical status (presence of uremic symptoms, nutritional status, and daily life activities) (Table 38.3) [70–74].

The IDEAL study was specifically designed to evaluate whether the timing of the initiation of maintenance dialysis influenced survival among CKD patients [62]. Patients were randomly assigned to initiate dialysis early (eGFR 10–14 ml/min/1.73 m^2) or assigned to the late-start group (eGFR 5–7 ml/min/1.73 m^2). The primary outcome was all-cause mortality. During the follow-up period, 152 of 404 patients in the early-start group (37.6%) and 155 of 424 in the late-start group (36.6%) died (HR with early start group 1.04, 95% CI 0.83–1.30, $P = 0.75$). The time of dialysis did not influence secondary events (cardiovascular, infectious) or quality of life. The study concluded that planned early initiation of dialysis in patients with stage 5 CKD was not associated with an improvement in survival or clinical outcomes. Following publication of the IDEAL study, several observational studies have been published about timing of dialysis initiation [61, 75–77]; most did not show benefit with early initiation and some even reported harm when treatment was started early. This suggests that presence of comorbidities rather than level of eGFR at

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Table 38.3 Guideline recommendations on vascular access.

Group	Year	Recommendation statements	Strength and evidence of recommendation
Canadian Society of Nephrology [63]	2006	**Planning for vascular access, access timing, placement, and maturation** • Preserve arm veins suitable for placement of vascular access. • Establish AVF when the patient has an eGFR of 15–20 ml/min and progressive kidney disease.	GRADE: D (opinion) GRADE: D (opinion)
		Preferred access type • The preferred type of vascular access is a radio-cephalic native vessel AVF.	GRADE: C
National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) [64]	2006	**Planning for vascular access, access timing, placement, and maturation** • In patients with CKD stage 4 or 5, forearm and upper-arm veins suitable for placement of vascular access should not be used for venipuncture or for the placement of intravenous catheters, subclavian catheters, or peripherally inserted central catheter lines. • A fistula should be placed at least 6 months before the anticipated start of HD treatments. This timing allows for access evaluation and additional time for revision to ensure a working fistula is available at initiation of dialysis therapy. • A graft should, in most cases, be placed at least 3–6 weeks before the anticipated start of HD therapy. Some newer graft materials may be cannulated immediately after placement.	GRADE: B
		Preferred access type • The access should be placed distally and in the upper extremities whenever possible. Options for fistula placement should be considered first, followed by prosthetic grafts if fistula placement is not possible. Catheters should be avoided for HD and used only when other options listed are not available.	Not graded
European Renal Best Practice Advisory Board (ERBP)/European Renal Association – European Dialysis and Transplant Association (ERA-EDTA) [65]	2007	**Planning for vascular access, access timing, placement, and maturation** • Potential chronic HD patients should be ideally referred to the nephrologist and/or surgeon for preparing vascular access when they reach stage 4 of their CKD (eGFR <30 ml/min/1.73 m^2) or earlier in case of rapidly progressive nephropathy or specific clinical conditions such as diabetes or severe peripheral vascular disease.	Evidence level: III
		Preferred access type • Autogenous AVF should be preferred over AVG and AVG should be preferred over catheters. • The upper extremity AV fistula should be the preferred access and should be placed as distal as possible.	Evidence level: III
The Society for Vascular Surgery [66]	2008	**Planning for vascular access, access timing, placement, and maturation** • We recommend that patients with advanced CKD disease (late stage 4, MDRD <20 to 25 ml/min) who have elected HD as their choice of renal replacement therapy be referred to an access surgeon in order to evaluate and plan construction of AV access.	GRADE 1 recommendation, very low-quality evidence
		Preferred access type • We recommend the placement of forearm autogenous AV access as the first choice for primary access for HD.	GRADE 1 recommendation, very low-quality evidence

(*Continued*)

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Table 38.3 (Continued)

Group	Year	Recommendation statements	Strength and evidence of recommendation
Renal Association Clinical Practice Guideline on Vascular Access for Hemodialysis [67]	2015	**Planning for vascular access, access timing, placement, and maturation** • We suggest that all patients that may require HD should have education on forearm vein preservation. • We recommend that the exact timing of placement of vascular access will be determined by rate of decline of renal function, comorbidities, and by the surgical pathway.	GRADE 2 recommendation, low-quality evidence GRADE 1 recommendation, moderate quality evidence
		Preferred access type • We recommend that all patients with ESKD who commence HD or are on long-term HD should dialyze with an AVF as first choice, an AVG as second choice, a tunneled venous catheter as third choice, and a nontunneled temporary catheter as an option of necessity.	GRADE 1 recommendation, high-quality evidence
Japanese Society for Dialysis Therapy [68]	2011	**Planning for vascular access, access timing, placement, and maturation** • If HD has been selected as the treatment for ESKD, the nephrologist should explain the role and importance of vascular access in this treatment and refer the patient to an access surgeon as soon as possible. • Vascular access construction should be considered when eGFR is <15 ml/min/1.73 m^2 (CKD stages 4 and 5) as well as considering clinical conditions; in patients with diabetic nephropathy, who have a tendency to show overhydration, vascular access construction should be considered at a higher eGFR.	Opinion, not graded Opinion, not graded
		Preferred access type • AVF of the wrist or the anatomical snuff box would be the first choice, but the site of vascular access construction should eventually be determined by a comprehensive evaluation of the patient's background, general conditions, and local conditions.	GRADE 1 recommendation, moderate quality evidence
Clinical Practice Guidelines of the European Society for Vascular Surgery [69]	2018	**Planning for vascular access, access timing, placement, and maturation** • Referral of CKD patients to the nephrologist and/or surgeon for preparing vascular access is recommended when they reach stage 4 of CKD (eGFR <30 ml/min/1.73 m^2), especially in cases of rapidly progressing nephropathy. • A permanent vascular access should be created 3–6 months before the expected start of HD treatment.	GRADE 1 recommendation, very-low quality evidence GRADE 1 recommendation, moderate quality evidence
		Preferred access type • An autogenous AVF is recommended as the primary option for vascular access.	GRADE 1 recommendation, high quality evidence

AV, arteriovenous; AVF, arteriovenous fistula; AVG, arteriovenous graft; CKD, chronic kidney disease; ESKD, end-stage kidney disease; eGFR, estimated glomerular filtration rate; HD, hemodialysis; MDRD, modification of diet in renal disease.

initiation could be associated with patient outcomes [77–79]. Given that residual renal function is a key determinant of outcome and is better preserved with PD, some studies have assessed the effects of early-start compared with late-start dialysis on clinical outcomes in PD patients [80, 81]. In a cohort of 8047 incident PD patients who started dialysis therapy in 2001–2009 in Canada, Jain et al. reported that in comparison with the late-start group, the overall mortality rate was not higher for the early-start (adjusted HR 1.08, 95% CI 0.96–1.23) or mid-start (adjusted HR 0.96, 95% CI 0.86–1.09) groups [80]. Their study conclusion, that early initiation of PD therapy (eGFR >10.5 ml/min/1.73 m^2) is not associated with increased mortality, was divergent to most observational studies assessing HD.

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Put together, it will be more beneficial if choice of dialysis modality and timing of commencement are determined on an individual basis that combines patient preference and lifestyle considerations while integrating medical factors and availability of resources and support, rather than comparison of survival outcomes [79].

Preparation for transplantation is addressed elsewhere in this textbook (Chapters 56 and 57). Unless there is absolute certainty about a patient's prospect for pre-emptive live donor kidney transplantation, it is preferable to provide dialysis preparation in parallel with or as an alternative to transplantation evaluation [59].

Preparation for Hemodialysis and Vascular Access

An integral component of dialysis is preparation and initiation. Hemodialysis as an extracorporeal form of RRT requires access to the circulatory system (i.e. vascular access) for blood to be circulated through the extracorporeal membrane (i.e. the dialysis membrane) (Table 38.3). Selection of the optimal type of vascular access can be challenging as there are various factors that need to be taken into consideration [82]. These elements include health-system associated factors, principal among which include the timing of referral of the CKD patient from primary care to the nephrologist or referral from nephrology care to the vascular access team, patient-related factors, such as the patient's preferred choice, age, and comorbidities (e.g. diabetes mellitus, obesity, peripheral vessel disease), and institutional availability/accessibility to the technical expertise required in creating and revising the vascular accesses should the need arise.

The timing of referral of the CKD patient to the nephrologist significantly influences the type of access incident HD patients commence therapy with. Clinical practice guidelines recommend that in preparing CKD patients for HD, arteriovenous (AV) access should be created well in advance of the anticipated start time of HD [63, 66, 67, 74, 83]. The guidelines also recommend that CKD patients be referred early, with the exact eGFR cut-offs varying among guidelines. They also advocate an even earlier referral for stage 4 CKD patients with known comorbidities as these may influence the outcome of access creation. There are three main vascular access options for HD, including (in order of preference) native arteriovenous fistulae (AVF), arteriovenous grafts (AVG), and central venous catheters (CVCs). AVFs remain the preferred initial option over AVGs, while CVCs are the least preferred except in special circumstances, for example high-risk of AV complications or the elderly with limited life expectancy or personal preference [84]. Arteriovenous access options (AVG or AVF) are preferred over CVCs as they have comparatively lower risks of infection, thrombosis, or stenosis of central veins [85]; in addition, they deliver superior blood flow rates which in turn contribute to better clearance of uremic wastes. For instance, an AVF provides blood flow rates of up to 500 ml/min with relatively low complication rates [86]. In addition, AVF is the most cost-effective vascular access option as it is associated with relatively lower infection rates and need for endovascular revision [87–89]. It is also recommended that AVFs should preferably be created using more proximal vessels with the aim of preserving the distal vessels for later use in the event of a failed proximal AVF (Table 38.3) [63–66, 68, 69]. Some have challenged the assertion that AVFs are superior or should be the preferred choice of access [90, 91]. They argue that various comparisons between access types are subject to high degrees of bias due to their observational design and suggest that such comparisons are unable to account for other patient factors which likely contribute to poor outcomes seen in patients treated with catheters [92, 93].

Although AVF is the preferred vascular access type, its use at dialysis initiation has shown marked global variability. Astor et al. in the Choices for Healthy Outcomes in Caring for End-Stage Renal Disease (CHOICE) study demonstrated that only about one-third of the proportion of patients referred early to their nephrology service within the prior 12 months started HD with an AV (AVF/AVG) access [94]. Data from the Dialysis Outcomes and Practice Patterns Study (DOPPS) [95] indicate that AVF use among incident dialysis patients is highest in Japan, where 84% of patients initiated dialysis with an AVF. This contrasts with 28% of patients in the United States and 19% in the Gulf Cooperation Council countries such as Kuwait and Bahrain; 50–60% of most European countries report dialysis initiation with an AVF [94]. The Fistula First Breakthrough Initiative (FFBI) of the Centers for Medicare and Medicaid Services (CMS), initiated in 2003, is a set of strategies based on the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) Clinical Practice Guidelines for Vascular Access with the aim of promoting more AV vascular access use among incident and prevalent HD patients. It has set a target of 50% AVF use among incident HD patients. One of the core strategies of the initiative in attaining this objective is the timely referral of the CKD patient to a vascular surgeon for AVF assessment and placement [66, 96].

As well-defined as the objective and benefits of establishing an autogenous vascular access route at dialysis initiation are, there are patients for whom such access may not be a preferred option, for example the elderly. As the global population of elderly CKD patients increases, the incidence rates of ESKD in the elderly population aged 65 years and above will likewise increase [2]. This translates to an older population of patients with a high burden of comorbidities,

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such as diabetes mellitus, peripheral vascular disease, and congestive heart failure, requiring the establishment of vascular access to initiate dialysis. Age and comorbidities are known negative determinants of autologous AV access maturation and functionality [77, 79, 97]. With an all-cause mortality rate of 31% per annum [98], death becomes a competing risk for fistula maturation and cost-effectiveness in the elderly [99]. There are no specific recommendations for vascular access type in the elderly; however, the suitability of the fistula first initiative has been questioned [100].

Preparation for Peritoneal Dialysis

As is the case with commencing HD, early referral is key to preparing the patient who has made the choice of PD. It is recommended that potential PD patients should be referred at the latest 4 months prior to the anticipated start of dialysis [101]. This period affords the opportunity for PD education and home visits by a home PD team to assess the suitability of the patient's living conditions for PD and the availability of adequate storage space for PD supplies. In situations where suitability of the home is suboptimal, necessary modifications may be made in time. In addition, early referral provides ample time to establish PD access and obviates the need for bridging HD therapy.

A functioning PD catheter is a crucial requirement to successfully starting PD. Current guidelines suggest that PD access be established at least 2 weeks before the start of dialysis [102, 103]. This time allows for the healing of the catheter insertion site, training of the patient on the peculiarities of the PD technique such as catheter handling and care, and carrying out supervised exchanges. For the patients whose catheter will not be used soon, it can be buried in the anterior abdominal wall until exteriorization at that time when PD is about to be commenced.

Conclusion

Early referral and involvement of the nephrologist are important to enable adequate preparation of CKD patients who progress to requiring dialysis. A multidisciplinary approach to patient preparation for dialysis is encouraged and should be individualized on a basis that combines patient preference and lifestyle considerations, while integrating medical factors and availability of resources and support. The approach should also include comprehensive patient education that allows for shared decision-making on choice of dialysis modality. Early referral also enables adequate time to prepare for successful creation and maturation of a native AVF (or other vascular access options) in patients who have opted for HD. Although guidelines published after the IDEAL study suggest that dialysis be initiated late, for patients who have opted to start treatment with PD or in places where PD is favored dialysis should be initiated at higher GFR when patients still have residual renal function as this have been shown to be associated with better patient outcomes.

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39

Choice of Hemodialysis or Peritoneal Dialysis for Kidney Replacement Therapy

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Introduction

The issue of timing of initiation of dialysis was first raised by Bonomini et al. in the 1970s [1–3]. They reported the highest survival rate in hemodialysis (HD) patients with a residual kidney function (measured by creatinine clearance) between 15 and 21 ml/min. However, criteria for the selection of patients for dialysis based on residual kidney function were not provided. The issue of an "earlier" start, which means with a higher glomerular filtration rate (GFR) than the usual threshold of 5–10 ml/min/1.73 m^2, reappeared again in the late 1990s when the process of developing guidelines for dialysis was started.

The choice of dialysis modality at the initiation of kidney replacement therapy has also been studied and discussed extensively in recent decades. There is, however, still no final consensus on whether HD or peritoneal dialysis (PD) treatment modality gives the best results. Consequently, both options have to be weighed in individual patients according to their specific needs, preferences, and clinical characteristics, with the aim of providing a patient-tailored kidney replacement therapy.

In this chapter, an overview is given of the current literature on the optimal timing of dialysis initiation and on the best dialysis modality choice.

Early Start or Timely Referral for Dialysis Initiation

A distinction should be made between the timing of referral to a nephrologist and the timing of initiation of dialysis treatment. Failure to make this distinction has confused the discussion. It should be emphasized that all studies on late referral to a nephrologist are either retrospective studies, based on surveys, or prospective cohort studies; nevertheless, the results are strikingly similar. Late referral for maintenance dialysis is associated with increased mortality [4–12] and decreased quality of life (QoL) [13, 14]. The excess mortality associated with late referral was independent of demographic characteristics, socio-economic status, and comorbidity. Moreover, late referral influenced the dialysis modality choice; patients who obtained predialysis care had a stronger preference for PD than patients who did not, the so-called late referrals [15]. In addition, patients who were referred late and started with PD were more likely to switch to HD during the first 6 months compared with patients who were referred in a more timely manner [16]. Despite all the evidence pointing to a beneficial effect of timely referral to a nephrologist, almost one-fourth of patients were referred less than 1 month before the start of dialysis in a survey of eight different European countries [17].

Guidelines and Studies on When to Initiate Dialysis Treatment

The timing of initiation of dialysis has been the subject of many opinion-based guidelines. A summary of international guidelines is presented in Table 39.1. The US National Kidney Foundation Dialysis Outcomes Quality Initiative (K/DOQI) Workgroup on Peritoneal Dialysis published an opinion-based guideline on the initiation of chronic dialysis treatment in 1997 [22]. The workgroup advised that dialysis should be initiated when renal Kt/V_{urea}

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Table 39.1 Guideline recommendations on the timing of initiation of maintenance dialysis in patients with end-stage kidney disease (ESKD), based on GRADE.

Group	Year	Recommendation statement	Strength and evidence of recommendation
European Renal Best Practice advisory board (ERBP)/European Renal Association – European Dialysis and Transplant Association (ERA-EDTA) [18]	2011	• In patients with eGFR <15 ml/min/1.73 m^2, dialysis should be considered when there is one or more of the following: symptoms or signs of uremia, inability to control hydration status or blood pressure or a progressive deterioration in nutritional status. It should be taken into account that the majority of patients will be symptomatic and need to start dialysis with eGFR in the range 9–6 ml/min/1.73 m^2.	Grade: strong recommendation, high-quality evidence
		• High-risk patients (e.g. diabetics and those whose renal function is deteriorating more rapidly than eGFR 4 ml/min//1.73 m^2 per year) require particularly close supervision. Where close supervision is not feasible and in patients whose uremic symptoms may be difficult to detect, a planned start to dialysis while still asymptomatic may be preferred.	Grade: strong recommendation, low-quality evidence
		• Asymptomatic patients presenting with advanced CKD may benefit from a delay in starting dialysis in order to allow preparation, planning, and permanent access creation rather than using temporary access.	Grade: weak recommendation, low-quality evidence
Kidney Disease Improving Global Outcomes (KDIGO) [19]	2012	We suggest that dialysis be initiated when one or more of the following are present: symptoms or signs attributable to kidney failure (serositis, acid-base or electrolyte abnormalities, pruritus); inability to control volume status or blood pressure; a progressive deterioration in nutritional status refractory to dietary intervention; or cognitive impairment. This often but not invariably occurs in the GFR range between 5 and 10 ml/min/1.73 m^2.	Grade: 2B
Canadian Society of Nephrology [20]	2014	For adults (aged >18 yr) with an eGFR of <15 ml/min/1.73 m^2, we recommend an "intent-to-defer" over an "intent-to-start-early" approach for the initiation of chronic dialysis. With the intent-to-defer strategy, patients with eGFR of <15 ml/min/1.73 m^2 are monitored closely by a nephrologist, and dialysis is initiated with the first onset of a clinical indication or a decline in the eGFR to 6 ml/min/1.73 m^2 or less, whichever of these should occur first. Clinical indications for the initiation of dialysis include the following: symptoms of uremia, fluid overload, refractory hyperkaliemia or acidemia, or other conditions or symptoms that are likely to be ameliorated by dialysis. In the absence of these factors, the eGFR should not serve as a sole criterion for the initiation of dialysis unless it is 6 ml/min/1.73 m^2 or less.	Grade: strong recommendation; moderate quality of evidence
Japanese Society for Dialysis Therapy [21]	2015	The judgment on the time to initiate HD is allowed when a residual renal function shows progressive deterioration and reaction to eGFR <15 ml/min/1.73 m^2 in spite of sufficient optimal conservative treatment. However, the decision of starting HD should be determined based on a comprehensive assessment of renal failure symptoms, daily life activities, and nutritional status, which are not relievable without HD treatment.	Grade: 1D
National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) [1]	2015	The decision to initiate maintenance dialysis in patients who choose to do so should be based primarily upon an assessment of 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.	Grade: not graded

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HD, hemodialysis.

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has fallen to 2.0/week. For a 70-kg man this equals a urea clearance of 8 ml/min, a GFR of 10 ml/min/1.73 m^2, and a creatinine clearance of 12 ml/min. A lower Kt/V_{urea} would only be acceptable when the normalized protein equivalent of nitrogen appearance, an index of protein intake in stable patients, was at least 0.8 g/kg of body weight/day and the patient was in a good nutritional state. These recommendations were retained in the update published in 2001. The clinical practice guidelines of the Canadian Society of Nephrology for treatment of patients with chronic kidney disease, published in 1999, were not significantly different from the US guidelines but set the target for the initiation of dialysis at a GFR of 12 ml/min/1.73 m^2 when symptoms were present. In addition, these guidelines state that dialysis should be started before the GFR drops below 6 ml/min/1.73 m^2 [23]. The European Best Practice Guidelines for PD recommend consideration of initiation of dialysis when the GFR is below 15 ml/min/1.73 m^2 in combination with evidence of poorly controlled conservative treatment. An absolute minimum value was set at 6 ml/min/1.73 m^2 [24].

At the time these guidelines were published many patients typically started dialysis at much lower clearances. In one study from the UK, the mean urea clearance was 3.9 ml/min [25]. A study from the United States reported that 63% of the patients had an estimated GFR between 5 and 10 ml/min/1.73 m^2, and 23% had an estimated value below 5 [26]. Although the aforementioned guidelines are not evidence based and are far from current practice, they have caused a trend toward earlier initiation of dialysis treatment [27, 28].

Observational cohort studies on the initiation of dialysis suffer two potential problems. First, the method used for GFR determination and, second, the effect of lead-time. Many cohort studies, often retrospective, used an estimation of glomerular filtration rate (eGFR) based on plasma creatinine, age, gender, and race, similar to the modification of diet in renal disease (MDRD) formula [29]. All investigations using the MDRD formula for eGFR reported associations between a high MDRD and increased mortality, despite corrections for possible confounders [30–32]. The use of the reciprocal plasma creatinine value in these analyses, instead of the creatinine clearance, is the most likely explanation because plasma creatinine is dependent on muscle mass and on glomerular filtration. The relative contribution of muscle mass to plasma creatinine will therefore be higher in the presence of severely impaired kidney function. Indeed a relationship between muscle mass and eGFR has been described in end-stage kidney disease (ESKD) patients at the initiation of dialysis, while follow-up confirmed the association between high eGFR values and mortality [33]. The obvious solution to avoid or diminish the effects of muscle mass on plasma creatinine is the use of creatinine clearance requiring timed urine collections or the use of a formula that includes an approximation of muscle mass, like the one developed by Cockcroft and Gault (C&G) in which body weight is included [34]. Using creatinine clearance, no effect of this parameter at the start of dialysis on mortality was found between patients who survived less than 1 year compared to those who survived more than 1 year on dialysis [35]. A comparison between 10-year patient survival after the start of dialysis between early (C&G >8 ml/min) and late (C&G <8 ml/min) starters showed a nonsignificant survival difference in favor of the early start group [36].

With the exception of Traynor et al. [36], none of the above-mentioned studies has taken lead-time bias into account. The lead-time is the period that late starters survive without dialysis, when compared with those who start earlier. When this difference is not taken into account, late starters will always have a survival disadvantage. The first study on the effect of lead-time bias was performed in 253 patients from the cohort of the Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD) [37]. The patients who started dialysis according to the US guidelines [22] survived longer than those who started at a lower urea clearance, but this difference was no longer present after correction for the lead-time. This correction was performed using a program developed for patients with a malignancy. The other published studies on effects of the lead-time on survival used a simpler approach, that is, analyzing patients not from the time of dialysis initiation, but from a predefined GFR, for instance 20 ml/min/1.73 m^2 [36, 38–40]. No difference in mortality was found after correction for the lead-time bias in the studies from Scotland [36] and the United States [39]. A survival difference was present in the study from Hong Kong [38], but here a population starting dialysis with a GFR of 9 ml/min/1.73 m^2 was compared to one with a lower GFR, in which dialysis was initiated acutely due to the presence of severe uremic symptoms. The study from the Netherlands is interesting because effects of lead-time correction were analyzed in a large cohort of patients with GFR measurements (mGFR) and eGFR [40]. Results for eGFR without lead-time correction showed no difference between early and late starters, but after correction early starters had an increased risk of death. Without correction for lead-time, mGFR early starters had a somewhat lower risk of death than late starters, but the difference disappeared completely after lead-time correction.

The only randomized controlled trial comparing early initiation of dialysis with a late start based on GFR estimations [41] confirmed the results of the observational cohort studies discussed above, including when subgroups (e.g. presence or absence of diabetes mellitus) were analyzed

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separately. It can therefore be concluded that no fixed GFR value to initiate dialysis can be identified, but that the value of clinical assessment cannot be underestimated. The development of severe uremic complaints should be avoided.

HD or PD as Initial Kidney Replacement Therapy

Dialysis modality choice at the initiation of kidney replacement therapy has been studied and discussed extensively in recent decades but still there is no final consensus on which treatment modality gives the best results. Consequently, both options have to be weighed in individual patients according to their specific needs, preferences, and clinical characteristics, with the aim of providing a patient-tailored kidney replacement therapy. Important outcomes for the evaluation of initial dialysis modality are patient survival, QoL, and values of biochemical parameters.

Patient Survival

The first study comparing continuous ambulatory PD with HD in incident patients was performed in the UK more than 30 years ago [42]. Using Kaplan–Meier analyses, the investigators showed that patient survival was not different between the two dialysis treatments during 3 years of follow-up. Since then, numerous survival comparisons between HD and PD treatment have been published, but their findings were inconsistent [43, 44]. Most studies performed in the last decade in Western countries showed either better survival for PD in the first period after the initiation of dialysis [45–49] or similar patient survival for both treatment groups [50–53]. In contrast, a large study performed in Korea showed higher mortality rates in PD patients than in HD patients [54]. Figures 39.1 and 39.2 show the dialysis "career" (including switches to other modalities and death) of patients who started either HD or PD in Europe between 1993 and 2007.

There are several factors that could potentially explain the differences in findings between these studies, including practice patterns, patient characteristics, and methodological issues.

Practice Patterns

Differences in dialysis modality-specific practice patterns between continents or countries may influence modality-specific patient survival. These practice patterns include general factors such as access to healthcare and organization of the healthcare system, but also more specific factors

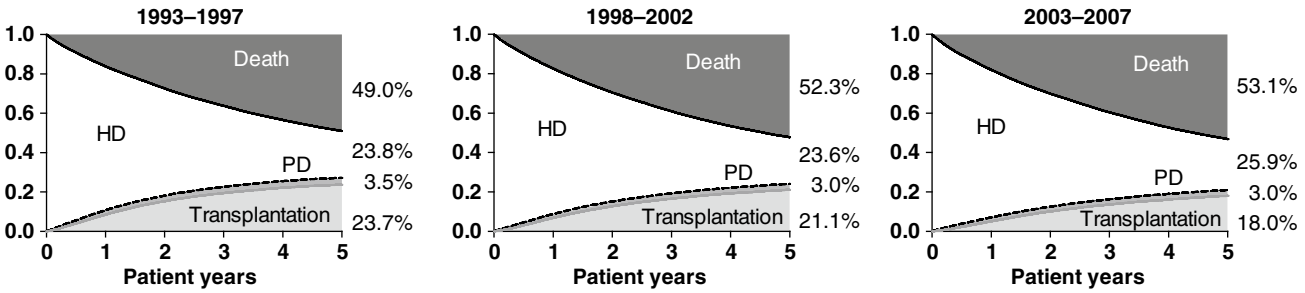

Figure 39.1 Unadjusted cumulative incidence survival curves for transfers to peritoneal dialysis or transplantation and death for patients who started hemodialysis in 1993–1997, 1998–2002, and 2003–2007. HD, hemodialysis; PD, peritoneal dialysis.
Source: Van de Luijtgaarden et al. [49] © 2016, Oxford University Press.

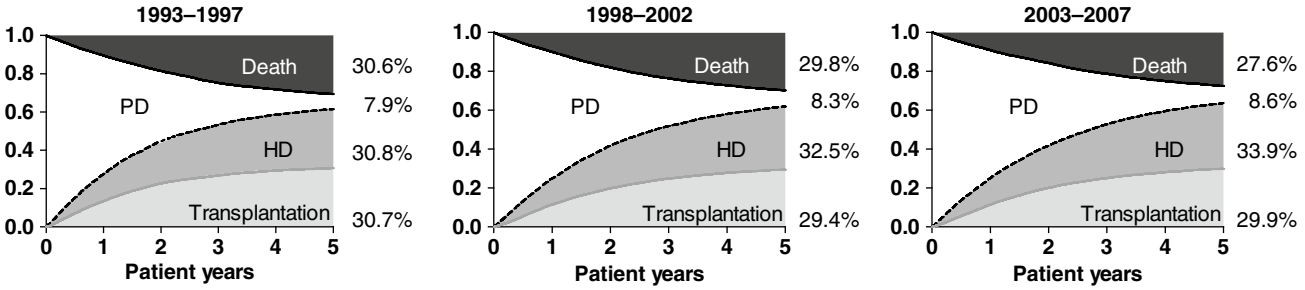

Figure 39.2 Unadjusted cumulative incidence survival curves for transfers to hemodialysis or transplantation and death for European patients who started peritoneal dialysis in 1993–1997, 1998–2002, and 2003–2007. HD, hemodialysis; PD, peritoneal dialysis.
Source: Van de Luijtgaarden et al. [49] © 2016, Oxford University Press.

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that may contribute to the efficiency and quality of the dialysis offered, such as the HD treatment time and vascular access type, peritoneal catheters, and the dialysis fluids used. However, the results provided in most comparative studies do not allow evaluation of the extent to which HD and PD were performed in a state-of the-art manner. For example, in many survival comparisons the type of vascular access used for HD is not included in the analyses, whereas it was shown in a Canadian cohort that the type of vascular access plays an important role in the relationship between dialysis modality and mortality [55]. Starting HD with a central venous catheter largely explained the higher early mortality risk of HD in this study. Another example is the omission of the type of dialysis fluid in the comparison of patient survival. Based on data from the Taiwan health insurance database, it was demonstrated that the inclusion of one icodextrin-based PD fluid in the usual PD schedule could attenuate the survival disadvantage for PD relative to HD in diabetic patients, particularly for those who were elderly [56].

An additional factor that is usually not taken into account in survival comparisons of HD and PD is whether the start of dialysis was "planned" or "unplanned." It has been postulated that patients who need to start dialysis urgently are at a high risk of death, and as they are treated predominantly with HD this could induce selection bias into the comparison of mortality between HD and PD patients. A French cohort study showed there was a significant increase (50%) in mortality risk among elderly patients (≥75 years) with an unplanned start of HD when compared to those with a planned start, which suggests a comparison between the two dialysis modalities would be more balanced after removing the unplanned HD starts [57]. Two Canadian studies confirmed these findings. In 2011, Quinn et al. showed that HD and PD were associated with similar survival in incident patients starting dialysis electively as outpatients [52]. More recently, Wong et al. reported that HD and PD are associated with similar mortality among incident dialysis patients who are eligible for both modalities [53]. They claim that to better reflect the outcomes for patients who have the opportunity to choose between HD and PD in clinical practice, future comparisons of dialysis modality should be restricted to patients who are deemed eligible for both modalities. Finally, most recently more and more attention has been paid to home-based therapies, including both HD and PD. Data from the Australia and New Zealand Dialysis and Transplant Registry (ANZDATA) demonstrated that outcomes on dialysis therapy are improving with time, and this improvement is most marked with home dialysis modalities, especially home HD, when compared to conventional in-center HD [58, 59].

Patient Characteristics

Several studies from different parts of the world that found overall similar effects for PD and HD or a beneficial effect of PD over HD also showed that patient survival on PD was worse in specific subgroups of patients: those who were diabetic and who were older (mostly over 55 years). For example, investigators from the Canadian Organ Replacement Register who included data on more than 35 000 incident dialysis patients found that overall adjusted survival remained similar for HD and PD, even in the most contemporary cohort [60]. After stratification for diabetic status, age, and sex, they found that nondiabetic patients in the youngest age group (<45 years) showed survival benefits on PD treatment, while there was no difference in mortality in the older age groups. However, survival on PD was worse than on HD among patients with diabetes, in particular in those with higher age, which confirms the findings from previous studies from the United States, Asia, and Europe [48, 50, 51, 57, 61, 62].

In addition, patient characteristics related to ethnicity could partly explain different study findings across populations. In the United States, it was shown that dialysis patients who are Hispanic have better survival rates compared to those who are white, across all age categories [63]. This survival advantage is also present in African-American patients, although it is limited to patients older than 40 years of age.

To illustrate the variation in findings from different parts of the world, the results of a selection of large renal registry studies comparing patient survival between HD and PD treatment are summarized in Table 39.2.

Methodological Issues

Ideally, the decision on which dialysis modality gives the best outcomes should be based on results of randomized controlled trials in which the allocation of the dialysis modality is not influenced by attitudes or preferences of the nephrologist and the patient. The first randomized controlled trial comparing HD and PD as initial kidney replacement therapy was conducted in the Netherlands between 1997 and 2000 [64]. However, pre-existing opinions held by patients and physicians on the best treatment option were often reason for not including patients in the trial. As a result, the study was underpowered (only 38 patients could be included) and thus unsuccessful. Despite this result, a new trial started in China in 2011 (trial registration NCT01413074, http://clinicaltrials.gov); 5 years later, it also was terminated. Consequently, outcomes in HD and PD patients can only be compared based on large-scale observational studies.

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Table 39.2 Comparison of mortality between HD and PD patients: a selection of recent large studies based on renal registry data.

Author, publication year (reference)	Country/region	Inclusion period	*N*	Effect
Asia				
Huang, 2008 [51]	Taiwan Renal Registry	1995–2002	48 629	Overall similar survival. PD better among nondiabetic patients and those ≤55 years; HD better among diabetic patients and those >55 years
Kim, 2014 [54]	Korean Health Insurance Review & Assessment Service database	2005–2008	32 280	Overall higher mortality on PD HD better among patients ≥55 years in all subgroups except those with no comorbidities and malignancy (similar survival regardless of age)
Europe				
Van de Luijtgaarden, 2016 [49]	European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) Registry	1998–2006	196 076	Overall PD better in first years after starting dialysis Similar survival for diabetic patients and those ≥65 years
North America				
Mehrotra, 2011 [50]	United States Renal Data System (USRDS)	1996–2004	624 426	Overall similar survival in the most recent cohorts Over time greater improvement in survival among PD patients relative to HD at all follow-up periods
Yeates, 2012 [60]	Canadian Organ Replacement Register (CORR)	1991–2004	46 839	Overall similar survival; PD better in first 18 months, HD better after 36 months Women with diabetes aged ≥65 years higher risk on PD
Oceania				
McDonald, 2009 [46]	The Australia and New Zealand Dialysis and Transplant Registry (ANZDATA)	1991–2005	27 015	Overall PD better in the first 12 months after starting dialysis, thereafter HD better Younger patients without comorbidities had mortality advantage with PD treatment, but other groups did not

N, number; HD, hemodialysis; PD, peritoneal dialysis.

An important issue regarding treatment comparisons is the difficulty of making causal inference based on observational studies. The most important weakness of observational studies is that selection bias by the clinician – also called confounding by indication – may occur. There are several strategies to reduce the influence of such selection bias. Of these, multivariable adjustment for potential confounders during statistical analysis is most commonly applied. In recent years, more and more research groups have started to apply advanced statistical methods in addition to the conventional methods of survival analysis (i.e. Kaplan–Meier and standard Cox proportional hazards models) to assess the associations between dialysis modality and mortality risk [44]. Such methods include time-dependent Cox regression models (e.g. in [46, 49]), marginal structural models (e.g. in [46, 47]), and the use of treatment propensity scores in statistical models by means of adjustment, stratification, or matching (e.g. in [46, 49, 59, 62]). The fact that so many different statistical methods are being applied can partly explain the inconsistency in study results.

Mehrotra et al. applied several of these statistical methods to compare the survival of HD and PD patients from the United States Renal Data System (USRDS) [50]. They concluded that in the most recent cohort (2002–2004), there was no significant difference in the risk of death between patients who started on HD or PD. These findings were confirmed by investigators from the Canadian Organ Replacement Register who used a similar approach in comparing the data of their incident dialysis patient cohort [60].

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Quality of Life and Biochemical Parameters

Although patient survival is an essential outcome, there are several other important outcomes that can and should be considered in the decision on which dialysis modality to choose. Many studies comparing all kinds of clinical outcomes between HD and PD have been performed. First of all, QoL is probably the most important outcome from the patient's perspective. However, only a few recent studies have compared the QoL between HD and PD patients. A meta-analysis published in 2017, in which only seven individual studies could be included, has not led to a unanimous conclusion [65]. Only some of the seven articles found significant differences between the two modalities; one showed a better QoL for PD patients, while two other studies found the best QoL in patients receiving HD.

In addition to QoL, there are many other outcomes that can be considered in the choice between the two dialysis modalities. One such outcome is the occurrence of renal anemia. A recent meta-analysis showed that both HD and PD have a similar effect on renal anemia in ESKD patients; the authors found no significant differences for levels of hemoglobin, ferritin, and transferrin saturation index between the two dialysis modalities [66]. A number of studies have shown advantages of PD, which were especially marked in the first years of treatment. These advantages include a better preservation of residual GFR [67–69] and better results after kidney transplantation with regard to delayed graft function [70, 71]. A systematic review and meta-analysis on the association between pre-transplant dialysis modality and transplant outcomes showed that patients who were treated with PD before their transplantation had a significantly lower incidence of delayed graft function and a better 5-year patient survival rate than those treated with HD before transplantation; there were no differences in the occurrence of acute rejection and graft survival [71].

Conclusion

Both for establishment of the optimal starting point for dialysis treatment and for dialysis modality comparison, the evidence base has needed to come from observational studies, despite their drawbacks, because as yet it has not been possible to perform randomized controlled trials. Up to now, these observational studies have indicated that no fixed GFR value to start dialysis can be identified. However, the value of clinical assessment cannot be underestimated and the development of severe uremic complaints should be avoided.

Overall, the treatment outcomes for HD and PD are very similar, even when sophisticated statistical methods are used. When specific patient subgroups were investigated, most studies showed that PD is associated with better survival for younger (mostly <55 years) and nondiabetic patients, but with worse survival for older and diabetic patient subgroups. These results indicate that both HD and PD can be considered as suitable initial kidney replacement therapy, depending on the patients' characteristics. Patients should be educated about potential advantages and disadvantages of both treatment modalities before the start of dialysis, so that they can make a well-informed choice together with their physician.

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Evidence-Based Nephrology

Second Edition

VOLUME II

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Preface

The synthesis of the totality of evidence in kidney disease was the original challenge we undertook when we conceived of the first edition of this evidence-based nephrology (EBN) textbook, thereby providing students of nephrology and practicing clinicians with a single convenient source of clinical evidence that had been passed through an evidence-based filter. More than 12 years have passed since the first edition, and so it is timely to revisit the challenge in the form of a second edition. The reasons for a second edition are principally three: the scale of new available data is substantial, newer methods of research synthesis have been developed, and there is a renewed focus on consumer engagement in general, including in the evaluation and management of kidney disease.

Scale of new data

Compared to the time of the first edition, the amount of new data is impressive. There are today more than 15 000 randomized controlled trials in nephrology published in approximately 30 000 reports, 11 300 more than in 2009, resulting in more confidence and precision around the estimates of intervention effects and new evidence in areas that were previously mostly evidence-free. These trials have also been summarized in systematic reviews, with over 6500 additional reviews in Medline since the first edition. Much of this new evidence is incorporated in three new sections of this textbook and multiple either new or entirely updated chapters.

Novel methods

Methods to assess the methodological quality of both systematic reviews and other study designs, including nonrandomized (case-control or cohort studies) and diagnostic test studies, have developed since the first edition. In addition, the number of syntheses of cohort studies has increased and the technique of network meta-analysis for comparing more than two interventions both directly (head to head) and indirectly (via a common comparator) has become more developed and is commonly encountered. These methods assist the summarizing and interpreting of evidence in key areas of decision-making, which is useful to patients, healthcare providers, and policy-makers.

Using these methods, organizations including the Cochrane Kidney and Transplant group and several guideline agencies have committed on a large scale to summarize the evidence and provide timely updates of established and emerging new evidence, making research findings more manageable and reliable for end users. Much of this work has been included in this edition of the textbook. We hope this will allow the end-user to both access best evidence from this diversity of resources as summarized by chapter authors and to become more familiar with how the newer techniques and resources contribute to a practice that is informed by best evidence.

Consumer engagement

Recently, there has been increasing recognition of the critical importance of engaging the end-users in research to ensure relevance and uptake. In particular there have been large-scale efforts to engage patients in all stages of research, including the evidence synthesis process and the dissemination of findings. For example, the Cochrane Kidney and Transplant group now has a patient editor, whose role includes translating scientific outputs into plain language summaries to simplify the "medical jargon" and make evidence easily accessible to people without a medical background, as well as prioritizing review topics. The Standardized Outcomes in Nephrology (SONG) initiative was launched in 2014 to establish the core outcomes to be reported in all trials in chronic kidney disease, based on a consensus among patients, caregivers, health professionals, and policy-makers. This initiative has emphasized patient-centered research and improved clinical outcomes in nephrology, ensuring that the outcomes measured and reported in clinical trials and other forms of research are relevant and meaningful to patients and increase the acceptability, transparency, and generalizability of the results in this population. New studies assessing these

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outcomes are now being developed, with advancement of knowledge which could be incorporated into this edition of the textbook.

In short, compared to the previous version published in 2009, this updated textbook includes 20 new chapters and three new sections, covering supportive care and patient-centered care and outcomes. In addition, every chapter that was in the first edition has been extensively updated. Specifically, the new textbook covers epidemiology, acute kidney injury, primary diseases of the kidney, secondary diseases of the kidney, chronic kidney disease and complications, hemodialysis, chronic kidney disease stage 5, peritoneal dialysis, supportive care, transplantation, electrolytes and acid-base disorders, and patient-centered care and outcomes for both adult and pediatric patients. This effort was undertaken by existing and new authors and section editors, whom we would like to thank for their extensive work.

Giovanni Strippoli has joined as the third co-editor of *Evidence-based Nephrology*. Altogether, we hope that we have produced an even better evidence-based nephrology tool, where each chapter provides a clear foundation of the topic that is supported by the best current evidence.

We believe that this updated textbook more broadly covers available evidence and addresses crucial clinical questions regarding the treatment and care of people with all stages of chronic kidney disease, including people undergoing any form of dialysis (hemodialysis or peritoneal dialysis), those requiring kidney transplantation, and pediatric patients.

Inherently a textbook of this nature will always manifest potential limitations. We acknowledge that a textbook is unable to collect all new evidence in real time, and, like all of healthcare internationally, the COVID-19 pandemic did impact this book, specifically the publication timelines as contributors had to contend with major challenges. The inclusion of nonrandomized studies to maximize relevance and comprehensiveness has added complexity in the methods and may lead to residual uncertainty in the estimate of intervention effects. Finally, we focused on empiric evidence for management decisions and so pathophysiological mechanisms of chronic kidney disease and its treatment were not considered in detail. We have attempted to include economic evaluations where particularly relevant for national and international management guidelines.

In the true spirit of evidence-based medicine, we hope that this edition of *Evidence-based Nephrology* will continue to push the specialty toward greater reliance on the totality of evidence and the generation and utilization of evidence that is the least biased and the most precise to inform clinical decision making. To the material detailed in all the chapters we would expect that our readers will add, through their own judicious application of evidence-based medicine principles, their local context, and incorporate their patients values and preferences, given that objective evidence is rightly only one consideration in the delivery of true patient-centered care. Additionally, a textbook like this can at best be only one of several resources for the evidence-based medicine practitioner, and should be supplemented with current methodologically rigorous and transparent clinical practice guidelines. We hope this effort will provide a core resource for the evidence-based nephrology practitioner who is otherwise limited by time constraints from researching every question that may arise daily in the care of patients.

We certainly wish that students and evidence-based nephrology practitioners will benefit from this updated edition in the search for answers to questions that arise in daily care and their ambition to deliver the best care possible.

Jonathan C. Craig
Donald A. Molony
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Part 6

Hemodialysis

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40

Modalities of Extracorporeal Therapy

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Introduction

Despite the complexity of hemodialysis (HD), the theoretical principles are relatively simple (Box 40.1). Blood and dialysis fluid are circulated on the opposite sides of a semipermeable membrane (the dialysis membrane), which permits the passage of water and smaller solutes, but restricts the passage of larger molecules. The provision of clinically adequate HD is for the most part dependent on water quality, dialysate composition, dialysis access, the presence and extent of treatment monitoring, and delivery and modality of blood purification.

Dialysis membranes are one of two key components that define the modality of blood purification, the other being the hydrostatic pressure gradient across the membrane itself (Table 40.1). The most important operating characteristic of dialysis membranes is their permeability to water. Low flux HD, high flux HD, and hemodiafiltration (HDF) are modalities characterized by increasing convective clearance of larger solutes in addition to the usual diffusive clearance of small solutes. The convective process relies on solvent drag by the passage of water across the membrane, and therefore greater membrane flux or permeability to water. Of note, the relative differences in clearance between all of these modalities of blood purification are large, although the absolute differences relative to native kidney function are small (Box 40.2).

The two other practiced forms of extracorporeal blood purification, hemofiltration and acetate-free biofiltration, are seldom used and will not be discussed in this chapter.

In this chapter, we summarize the published studies of hemodialysis membrane type and hemodialysis modality, and provide recommendations for nephrologists responsible for hemodialysis care.

Box 40.1 Dialysis Key Features

Dialysis modality	Membrane qualities	Solute removal
• Low-flux HD • High-flux HD • HDF	• Synthetic versus cellulosic • Low-flux, high-flux, super-flux	• Diffusion • Convection • Adsorption

HD, hemodialysis; HDF, hemodiafiltration.

Epidemiology

The origins of modern extracorporeal techniques for the treatment of end-stage kidney disease (ESKD) can be traced back to the early twentieth century, where rudimentary devices were used to remove fluid and solutes from blood in animal experiments. However, these early efforts were significantly limited by the insufficient effectiveness of the blood purification treatment. Modern efforts using HD became possible in the 1960s, with technological advances allowing improved dialysis membrane quality and mass production, along with improvements in anticoagulation and dialysis access.

Today HD is routinely applied to patients as an indefinite life-sustaining treatment for ESKD. Worldwide there are currently in excess of three million patients receiving HD and this number is projected to increase significantly, mostly due to the increased access to care in developing

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Table 40.1 Membrane type and modality.

Treatment	Recommendation	Certainty of evidence	Strength of recommendation
Hemodialysis (HD)	We suggest a synthetic, biocompatible, high-flux dialysis membrane can be used for hemodialysis rather than a low-flux membrane, to reduce cardiovascular mortality, although providers and patients may reasonably choose a low flux membrane due to the low certainty of effects on cardiovascular mortality and other outcomes.	Low	Weak
Hemodiafiltration (HDF)	We suggest HDF may be used rather than conventional HD to reduce cardiovascular mortality and reduce frequency of intradialytic hypotensive events, although patients may reasonably choose not to due to the low certainty evidence for improved clinical outcomes.	Low (cardiovascular mortality) or very low (dialysis-related hypotension)	Weak

GRADE assessment of the certainty of the evidence [1]: High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different* is low. Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different* is moderate. Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different* is high. Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different* is very high. *Substantially different = a large enough difference that it might affect decision-making.

Box 40.2 Relative Small and Large Solute Clearance for Different Stages of CKD and Dialysis

Native renal or RRT	Fluid control (%)[a]	Equivalent small uremic toxin clearance (EKRc)[b]	Equivalent large uremic toxin clearance (EKRc)[c]
Low-flux HD	5–10	10–15	3–3.5
High-flux HD	5–10	10–15	3.5–4
High-volume HDF	5–10	10–15	4–5
PD	100	8–12	1–2
Intensive HD	10–30	20–30	5–10
Severe CKD	100	15–30	15–30
Moderate CKD	100	30–60	30–60
Normal kidneys	100	> 60	> 60

CKD, chronic kidney disease; PD, peritoneal dialysis; RRT, renal replacement therapy.
[a] Hours per week of ultrafiltration as a percentage of 168.
[b] EKRc for urea, ml/min.
[c] EKRc for β2-microglobulin, ml/min.

nations. For most patients routine HD involves three treatment sessions per week, of 4–5 hours of treatment per session, although practice can and does vary considerably between countries. Most treatments are performed in hospital or free-standing community facilities, with a small percentage occurring as home-based HD.

Pathophysiology

Dialysis Membranes

Dialysis membranes permit the movement and removal of solutes and water during dialysis. Membranes have been generally classified based on their composition (cellulosic vs. synthetic) and permeability to water (high vs. low flux). Super-flux membranes, with markedly increased water permeability and middle molecule clearance, have become commercially available and are defined as medium cut-off (MCO) and high cut-off (HCO) membranes [1]. Dialysis membranes are not physiologically inert and make contact with the patient's blood, therefore they can elicit active biological responses in the patient. Although there is no formal definition of "bioincompatibility," such responses have long been recognized as device-related and clearly linked to adverse clinical outcomes.

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The Evolution of Dialysis Membranes

The first modern HD membranes were cellulose based, thin-walled, and functionally classified as low flux. Despite their functionality, there were two significant disadvantages of these membranes. First, the natural, cellulosic fibers were immune-reactive mainly as a result of exposed hydroxyl groups [2, 3] activating inflammatory pathways such as complement and inducing inflammatory mediators. This resulted in a classical inflammatory response syndrome, reduced dialysis tolerance, and dialysis-related cachexia. Second, they only permitted the passage of small solutes (MW < 500 Da). This inability to remove larger molecules (in particular β2-microglobulin, MW 11 800 Da) was implicated in the subsequent development of dialysis-related amyloidosis, especially in very long-term HD patients [4].

The evolution of membranes in general occurred in two directions, first to improve "bioincompatibility" and second to improve flux. Development largely focused on the large-scale production of synthetic membranes made from polysulfone, polyamide, polyarylethersulfone, and polymethylmethacrylate [5]. Such plastics are generally, but not always, more biocompatible and less biologically active. They can be spun into fibers with more consistent pore size and geometry compared to cellulose, allowing more precise molecular weight (MW) cut-off and therefore more predictable clearance of larger molecules [6]. Early synthetic membranes were considerably thicker than low-flux membranes, causing a degree of impediment to diffusion-based clearance. However, modern synthetic membranes are thinner, with excellent operating characteristics.

High-flux membranes have increased clearance of middle molecules (nominally β2-microglobulin), which in turn has been associated with a reduced incidence of symptoms on dialysis and long-term complications such as dialysis-related amyloidosis [7]. Initial concerns about the excessive cost of high-flux membranes have been largely negated in developed countries with near-universal adoption. In addition, decreased dialyzer reuse has led to large volume production and further decreased costs. However, these remain pertinent issues in developing countries with comparatively nascent dialysis infrastructure. The routine use of endotoxin filters in modern dialysis circuits, and overall improvements in dialysis water quality and water purification technology have largely mitigated concerns about back-filtration of dialysate contaminants to the patient's blood [8].

The Clinical Relevance of "Flux"

Formally, "flux" is defined by the ultrafiltration coefficient (K_{uf}) of a dialysis membrane, defined as the rate at which water crosses the membrane at a given transmembrane pressure (defined in ml/h/mmHg). The importance of flux is not the permeability of the water per se, but the fact that greater flux of water across the membrane during the course of HD or HDF treatment results in greater passage of larger molecules (nominally β2-microglobulin) through the dialysis membrane by the process of solvent drag. Informally, both of these operating characteristics are now used to discriminate low- from high-flux membranes. However, thresholds that define degrees of "flux" remain somewhat arbitrary. In the HEMO study, a high-flux dialysis membrane was defined as $K_{uf} > 14$ ml/h/mmHg and β2-microglobulin clearance of >20 ml/min, whereas low-flux membranes were defined as β2-microglobulin clearance of <10 ml/min [9]. More recent definitions normalize the K_{uf} to the membrane surface area (expressed in ml//h/mmHg/m [1]) and define β2-microglobulin in terms of the sieving coefficient (SC), which is a ratio of the solute in the filtrate compared to its plasma concentration. The Membrane Permeability Outcome (MPO) study defined high-flux as β2-microglobulin SC >0.6 and $K_{uf} \geq 20$ ml/mmHg/h [10]. The European Dialysis (EUDIAL) Working Group felt that a characteristic of middle molecule clearance should be incorporated in a modern definition of "high flux" in addition to the ultrafiltration coefficient of a membrane.

The agreed EUDIAL definition of a high-flux membrane is based on the MPO study and is $K_{uf} = 20$ ml/h/mmHg/m [2] and β2-microglobulin SC > 0.6 [11]. It is important to note that most of the studies comparing high- and low-flux, and HD and HDF did not use this definition.

Middle Molecule Clearance and Super-flux Membranes

The chronic inflammatory response seen in maintenance HD patients has been linked to accelerated atherosclerosis, endothelial dysfunction, increased advanced glycosolation end-product levels, protein-energy wasting, cachexia, and secondary immune deficiency [12–19]. These in part mediate the increased all-cause and cardiovascular disease (CVD) mortality seen in ESKD patients when compared to age-matched individuals without kidney disease. This chronic inflammatory response is multifactorial and can be attributed to the plastic consumables used during dialysis, dialysis membranes, disinfecting solutions, and water quality as well as the presence of endotoxins and uremia. All of these can directly or indirectly induce pro-inflammatory cytokines, many of which are large-middle molecules (TNF-α, IL-6, and IL-10), themselves poorly cleared with conventional high-flux HD [20]. The contribution of a dialysis membrane to this process can be viewed in terms of its

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contribution to inflammation (bioincompatibility) and potential for clearance of middle molecules during HD. The aim of increasing middle molecule clearance during HD has driven the development of super-flux membranes.

Middle molecules are a heterogeneous group of compounds broadly defined as having a MW of 500–60 000 D [21]. This includes the archetypal middle molecule marker β2-microglobulin and a plethora of other compounds that include cytokines, uremic toxins, growth factors, and hormones, which are generally further subclassified based on MW. Modern high-flux membranes are excellent at removing β2-microglobulin (MW 11800 D), but are poor at removing large-middle molecules (MW > 15 000 D) [22]. Therapies which combine convection with diffusion such as HDF (see below) have become an increasingly accepted method for increasing middle molecule clearance. Similarly, recent developments in membrane technology have enabled the development of super-flux membranes which are capable of clearing molecules with a MW of up to 50 000 D, which approximates and potentially surpasses the clearances provided by HDF [23, 24].

High cut-off membranes (HCO) were used clinically in the setting of kidney failure due to multiple myeloma to enhance the removal of kappa and lambda light chains (large-middle molecules) [25, 26]. These have a wide distribution of pore sizes and show variable clinical efficacy in the treatment of cast nephropathy. However, their use is associated with increased albumin loss and significant electrolyte abnormalities, e.g. hypophosphatemia. MCO membranes have been developed with a narrower range of distribution of pore sizes (Figure 40.1), below the MW of albumin (68 000 D). In theory these allow for more effective middle and large-middle molecule clearance, without excessive albumin loss [27]. What constitutes acceptable loss of albumin during HD remains unclear. Some albumin loss may in fact be beneficial due to the removal of protein-bound toxins. Super-flux membranes may provide us with a form of "enhanced" HD (when considered in terms of large-middle molecule clearance). The potential benefits of this new class of membranes, particularly when compared to existing convective therapies, requires further evaluation in clinical studies.

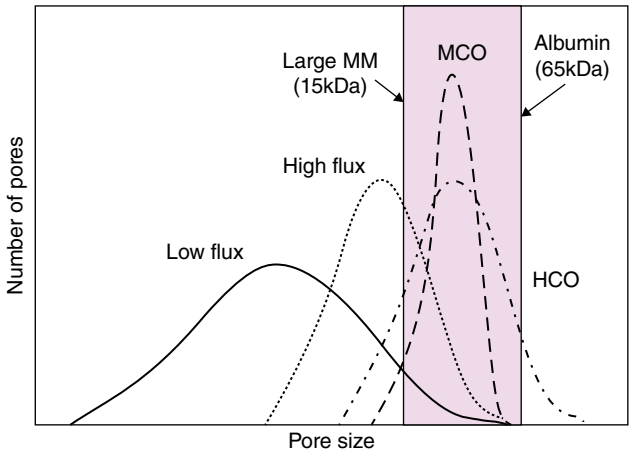

Figure 40.1 Schematic of pore size in dialysis membranes. MCO membranes (in pink) have been specifically designed to remove large middle molecule (compared to high-flux) membranes without excessive albumin loss (compared to HCO membranes). HCO, high cut-off; MCO, medium cut-off; MM: middle molecules. *Source:* From Wolley et al., CJASN 2018. ASN.

Dialysis Modality

HD is based on the diffusion of solutes across a semipermeable membrane and is highly effective at fluid removal, correcting acidosis and electrolyte disturbances, and removing small solutes and toxins. HD is less effective at removing middle and large-middle molecules, as effective diffusion is inversely related to MW. Convective therapies have been developed to overcome this problem by increasing the transport of larger molecules across dialysis membranes. HDF differs to conventional dialysis in that it involves the exchange of large volumes of fluid with the patient. Early convective therapies such as hemofiltration were subsequently combined with diffusion-based therapies in HDF, which is the most commonly used convective therapy across the world. Whilst HD remains the most commonly used dialysis modality worldwide, the uptake of HDF is increasing, particularly in Europe and Japan [28, 29].

Conventional HD

Conventional HD involves the use of a single-pump dialysis machine. Blood is drawn from the patient, passed through a semiporous hollow-fiber dialyzer of a given membrane type, and returned to the patient. At the same time, the dialysis solution (dialysate) is passed in a counter-current fashion through the dialyzer, on the other side of the dialysis membrane to the blood, in a single-pass fashion (meaning dialysate passes the membrane only once and then is discarded). The removal of excess extracellular fluid from the patient occurs by passage of the ultrafiltered extracellular fluid across the semiporous membrane from the blood compartment to the dialysate compartment. This is predominantly controlled by hydrostatic pressures but is also dependent on the porosity of the membrane and its ultrafiltration coefficient. High-flux membranes allow for the movement of more fluid than is desired, and this is balanced by back-filtration of dialysate back into the blood. In modern dialysis machines this is

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achieved with the use of ultrafiltration monitors which allow the setting of net fluid removal during each dialysis session. Solute removal is dependent on molecular size and weight, hydration radius, osmotic gradient, and electrical charge. Different dialyzer membranes, of different pore size and composition, will allow the passage of solutes at different rates, and more porous membranes allow the removal of larger molecules (see above). The predominant mechanism of removal, especially for smaller solutes, is movement through diffusion from blood into the dialysate. The other mechanism is convection, which occurs when dissolved solutes are removed as ultrafiltration occurs (also referred to as "solvent drag"). This latter mechanism is more important for larger molecules and is dependent on the porosity of the membrane. In conventional HD, most solute removal is by dialysis and ultrafiltration volumes are generally in the order of 6–8 l maximum (balanced by back-filtration within the dialyzer; Figure 40.2).

HDF

HDF differs from standard HD by incorporating a highly porous dialysis membrane that allows very high convective volumes. On-line HDF requires the use of a double-pump dialysis machine, utilizing a highly porous dialysis membrane that allows loss of high-volume ultrafiltrate into the dialysate compartment. The volume of ultrafiltrate lost is replaced by the infusion of ultrapure dialysate (UPD) into the patient's blood using the second, substitution fluid blood pump (Figure 40.3). The typical substitution volumes achieved in a standard post-dilution HDF should exceed 20 l, and any proposed benefit of HDF over high flux relies on effective convection volumes of at least 18–20 l. The European Dialysis Working Group (EUDIAL) has revised the definition of HDF incorporating both membrane properties (high flux as defined above) and convective volumes of least 20% of the total blood volume processed with fluid balance maintained by infusion of substitution fluid into the patient's blood [11].

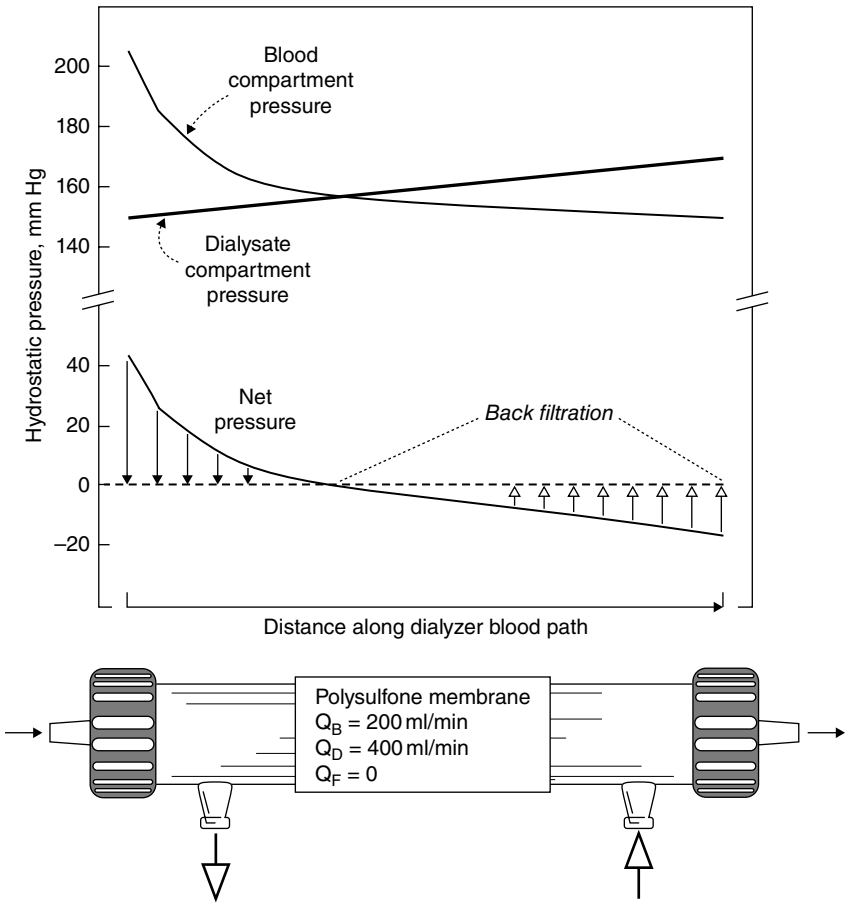

Figure 40.2 Schematic of fluid removal along a dialysis hollow fiber membrane. The net ultrafiltration volume is controlled by balancing the pressures, in effect by controlling negative pressure on the dialysate side of the membrane. *Source:* From Streicher, E., & Schneider, H. (n.d.). The Development of a Polysulfone Membrane. In Highly Permeable Membranes (pp. 1–13). © 1985, Karger Publishers.

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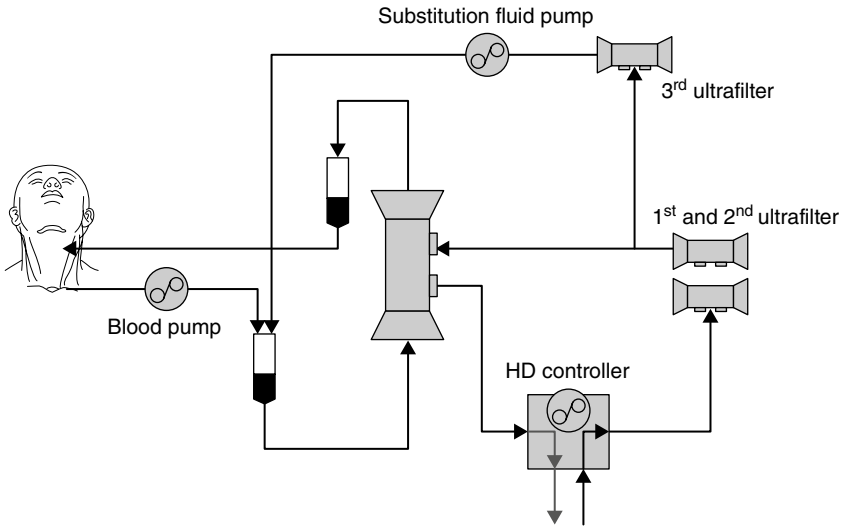

Figure 40.3 Schematic of the circuit used in HDF. This diagram represents predilution fluid replacement. Postdilution differs in the site of the entry of the replacement fluid (as the blood leaves the dialyzer, rather than prior to entry to the dialyzer).

The various types of HDF differ by the site of the dialysate replacement, which can be pre or post the dialyzer (or pre and post as "mixed" HDF), with differences around solute removal and the potential for excessive hemoconcentration. Predilution HDF (infusing the substitution fluid before the blood enters the dialyzer) dilutes the concentration gradient across the dialyzer, potentially decreasing small molecule clearance, but in clinical practice this is offset by greater ultrafiltration volumes (compared to postdilutional HDF), with the ensuing solvent drag resulting in similar clearances overall [30]. In post-dilution HDF the dialysate is infused downstream of the dialyzer (after dialysis has occurred), which optimizes the clearance of solutes through diffusion, and the high ultrafiltration rates limit the back-filtration that occurs in high-flux HD [31]. A limitation of this modality is that at high ultrafiltration rates there is excessive hemoconcentration within the dialyzer fibers, causing elevated transmembrane pressures, reduced clearances, and clotting of the dialysis circuit. To prevent this problem, the filtration fraction is generally limited to 20–25% of the total blood flow rate [32]. In modern dialysis machines, mixed dilution HDF allows for the infusion of dialysate both before and after the dialyzer, and the ratio of the infusion rates can be balanced to optimize clearances and minimize the adverse consequences of hemoconcentration. However, most observational and trial data are based on postdilution HDF.

The large convective component of HDF greatly enhances solute removal, but any improvement over conventional HD is mostly limited to middle and large-middle molecules.

As large volumes of dialysate are infused directly into blood lines, additional treatment monitoring considerations are needed. The first is the need for more accurate monitoring of fluid balance to ensure the balance of removed and replaced fluid equates with the desired fluid loss for the session. The second is the microbiological purity of the dialysate, with separate standards existing for HDF and HD, respectively.

Water Quality

Historically, poor water quality (from a variety of environmental, chemical, and microbiological factors) has been implicated in bio-incompatibility and adverse patient outcomes [33]. The quality of dialysis water has seen incremental improvements with advances in water purification, disinfection methods, and routine monitoring. The provision of high-quality dialysis fluids is now readily achievable in all modern dialysis units. The provision of high-quality dialysis water is arguably even more important in the provision of HDF, given the direct infusion of substitution fluid into the blood line. The advent of convective therapies has resulted in a new, more rigorous dialysis fluid quality standard, UPD, which is used for substitution fluids in HDF. The differences between standard and UPD dialysis fluids are defined by the International Organization for Standardization (ISO) in terms of terms of bacterial load, the total viable count in colony forming units per milliliter, and total the endotoxin load in endotoxin forming units per milliliter (Box 40.3).

Putative Benefits of HDF

It has been a long-standing supposition that the improved middle-molecule clearances (see above) observed with

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Box 40.3 Allowable Levels for Bacteria and Endotoxins in Dialysis Fluids

Contaminant	Standard dialysis fluid		Ultrapure dialysis fluid
	Maximum allowable level	Actional level (~ 50% of maximum level)	Maximum allowable level
TVC (CFU/ml)	<100	50	<0.1
Endotoxin (EU/ml)	<0.5	<0.25	<0.03

CFU, colony forming units; TVC, total viable count; EU, endotoxin units.
Source: Adapted from ANSI/AAMI/ISO. *ISO 11663 : 2009. Quality of dialysis fluid for haemodialysis and related therapies.*

HDF should translate to improved patient outcomes. Adding large convective volumes to standard (high-flux) HD improves the clearance of middle molecules, especially those in the 15 000–25 000 MW range, which includes a number of cytokines such as TNF-a, IL-1, IL-10, and IL-6 [34–36]. These have long been implicated in dialytic instability, bio-incompatibility, and poor dialysis outcomes, so their potential removal by HDF is an area of significant clinical interest. In the CONTRAST study, IL-6 and C-reactive protein (CRP) levels were lower in the HDF cohort compared to the conventional (low-flux) HD cohort [37]. However, in the FRENCHIE study there were no significant differences between HDF and high-flux HD over 24 months in serum levels of IL-6, IL-10, TNF-alpha, NT- N-terminal pro brain naturetic peptide (ProBNP), or high sensitivity cardiac troponin T (hs-cTNT) [38]. These results need further validation, and increased removal of cytokines may itself not be adequate if the stimulus for their induction is not addressed. Molecules in the large-middle molecule spectrum with MW 25 000–60 000 D remain poorly cleared by all HDF and high-flux HD therapies. The clearance of protein-bound solutes is generally not improved by HDF [39].

Cardiovascular instability remains a frequent clinical problem in patients on HD, and intradialytic hypotension has been increasingly associated with stunning of the myocardium and other vital organs such and the gut [40–43]. Anecdotally it appears that HDF may confer increased cardiovascular stability, but considerable debate continues as to whether this is indeed the case. Early observational and interventional studies provided mixed results with regards to cardiovascular stability and outcomes [44–46]. The results of two separate meta-analyses found that HDF reduces the incidence of symptomatic hypotension (compared to HD), with no significant difference in cardiovascular events or cardiovascular mortality [47, 48]. The recent FRENCHIE study, a randomized controlled trial (RCT) of older patients (>65 years), did not demonstrate a positive benefit for HDF over HD for the primary outcome of intradialytic tolerance. A small study using functional cardiac magnetic resonance imaging (MRI) studies during dialysis sessions found no difference in wall motion abnormalities and a number of cardiac parameters between high-flux HD and HDF [49]. The mechanisms underpinning any benefit for HDF have not been clearly elucidated but may relate to removal of cardioactive/vasoactive agents, such as interleukins and other vasoactive peptides. Alternatively, it may relate to thermal stability. This concept suggests that the large volume of infused dialysate prevents overheating during dialysis, thus preventing vasodilatation.

Treatment

High-flux Versus Low-flux on Cardiovascular Outcomes and Survival

A number of observational studies support an association between the use of high-flux membranes and improved survival outcomes in hemodialysis [50–53]. Three large RCTs were designed to provide further clinical evidence and these include the HEMO trial, MPO and the Multiple Interventions Related to Dialysis Procedures in Order to Reduce Cardiovascular Morbidity and Mortality in HD Patients (known as the EGE study) [10, 54, 55]. The details of these studies are outlined in Table 40.2.

A Cochrane meta-analysis pooled data from 33 randomized controlled trials and included 3820 participants. The results of the analysis are outlined in Table 40.3 [56]. Cardiovascular mortality was proportionally reduced by 17% in individuals receiving high-flux membrane dialysis compared to low flux dialysis (five studies, 2612 participants: risk ratio [RR] 0.83, 95% confidence interval [CI] 0.70 to 0.99) across a median follow up of 24 months. However, high-flux membranes did not reduce all-cause mortality, infection-related mortality, or hospital admissions compared to low-flux membranes. While the use of high-flux membranes reduced predialysis β2-microglobulin levels, insufficient data were available to reliably estimate the effects of membrane flux on carpal tunnel syndrome or amyloid-related arthropathy. In relation to surrogate outcomes, the data demonstrates that it is unlikely there is any

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Table 40.2 Major randomized controlled trial of high-flux versus low-flux membrane dialysis on clinical outcomes.

Study	Comparators	N	Follow-up	Primary results	Subanalysis	Comments
HEMO [9, 54] 2003, 15 USA centers	2–2 factorial study: high-flux HD vs. low-flux HD and low dose (achieved *Kt*/*V* 1.08) vs. high dose (*Kt*/*V* 1.4)	1846	0.8–6.6 years (mean 4.24) Lost to follow-up: 0/1846	No difference in primary and composite secondary endpoints Primary endpoint: RR for all-cause mortality high-flux vs. low-flux HD 0.92, 95% CI 0.81–1.05, $P = 0.23$ Secondary endpoints: (i) first hospitalization for cardiac causes or death from any cause, (ii) first hospitalization for infection or death from any cause, (iii) first 15% decrease in the serum albumin level or death from any cause, and (iv) all hospitalizations not related to vascular access	RR of cardiac death for high-flux HD vs. low-flux HD 0.80, 95% CI 0.65–0.99, $P = 0.042$ RR for composite of first cardiac hospitalization or cardiac death for high-flux HD vs. low-flux HD 0.87, 95% CI 0.76–1.00, $P = 0.045$ Survival benefits were seen in the high-flux HD if dialysis vintage >3.7 years RR 0.68, 95% CI 0.53–0.86, $P = 0.001$ Lower predialysis β2-microglobulin in the high-flux HD arms No difference in health-related quality of life between the groups	Patients are not blinded to the intervention Dialyzer reuse was permitted
MPO [10] 2008, 59 centers in Italy	Parallel RCT: high-flux vs. low-flux HD (stratified by serum albumin > or ≤4 g/dl) with a minimal dialysis dose of *Kt*/*V* 1.2	738	3–7.5 years Lost to follow-up: 191/738	No difference in primary and secondary endpoints Primary endpoints: all-cause mortality, HR 0.76, 95% CI 0.56 to 1.04, $P = 0.091$ Secondary endpoints: hospitalization due to all causes, infections, or vascular access related issues Lower accumulation of predialysis β2-microglobulin in high-flux HD group	Reduction in mortality in patients with serum albumin < 4g/l was significantly lower in the high-flux HD (p=0.032). RR 0.49, 95% CI 0.28–9.87, observed in high-flux HD Survival benefit in those with diabetes (combined type 1 and type 2 diabetes mellitus) observed in high-flux group	Enrolled incident patients only Initially inclusion criteria was serum albumin <4 g/l Due to slow recruitment, protocol was amended to include patients with serum albumin >4 g/l
EGE 2013, 8 centers, Turkey	2 × 2 factorial design, randomized to high-flux vs. low-flux, and ultrapure versus standard dialysate	740	1–50 months (mean 35.2 months)	No difference in primary endpoint Primary endpoints: composite of fatal and nonfatal CV events (myocardial infarction, stroke, unstable angina requiring hospitalization, and revascularization): HR 0.73, 95% CI 0.49–1.08, $P = 0.12$ Secondary endpoint: overall mortality Lower β2-microglobulin and time-averaged CRP in HF groups	High-flux HD group had lower CV event in those with AVF and among diabetic subjects The highest overall survival was observed in patients receiving dialysis using an AVF, treated with a combination of high-flux HD using ultrapure dialysate	Participants with substantial residual function were excluded from this study, this may increase the reported benefit from high-flux HD

ACM, all-cause mortality; AVF, arteriovenous fistula; CI, confidence interval; CRP, C-reactive protein; CV, cardiovascular; HF, high-flux membrane dialyzer; LF, low-flux membrane dialyzer.
Source: Data from Palmer et al. [56].

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Table 40.3 Summary of findings: high-flux HD compared to low-flux HD.

	High-flux hemodialysis vs. low-flux hemodialysis				
Outcomes	**No. of participants (studies)**	**Absolute number (95% CI) of patients affected per 1000 treated patients for 1 year**	**Relative effect (95% CI)**	**Quality of the evidence (GRADE)**	**Conclusion**
All-cause mortality	2915 (10)	Five fewer deaths (15 more to 20 fewer)	0.95 (0.87–1.04)	Low ●●○○	It is unlikely that high flux membranes reduce all-cause mortality
Infection-related mortality	2547 (3)	Not estimated	0.90 (0.71–1.14)	Low ●●○○	It is unlikely that high-flux membranes reduce infection-related mortality
Cardiovascular mortality	2612 (5)	15 fewer deaths (0–30 fewer)	0.83 (0.70–0.99)	Low ●●○○	High-flux membranes may reduce CV mortality
All hospital admissions	74 (2)	Not estimated	0.79 (0.52–1.20)	Very low ●○○○	It is uncertain whether high-flux membranes reduce all-cause hospital admissions
Dialysis-related hypotension	84 (1)	Not estimated	3.00 (0.13–71.61)	Very low ●○○○	It is uncertain whether high-flux membranes reduce intradialytic hypotension
Quality of life	1835 (2)	Not estimable	Not estimable	Very low ●○○○	It is uncertain whether high-flux membranes have benefits on health-related quality of life domains
Dialysis adequacy leading to trial withdrawal	155 (1)	Not estimated		Very low ●○○○	It is uncertain whether high-flux membranes have benefits on dialysis adequacy compared to low-flux membranes
Residual renal function (RRF)	RRF at end of study: 30 (1) Rate of decline: 20 (1)	Not estimated	1.10 ml/min (0.80–1.30) −0.13 ml/min/month (− 0.17 to – 0.09)	Very low ●○○○	It is uncertain whether high-flux membranes help preserve residual renal function
β2-microglobulin complication: carpal tunnel syndrome	20 (1)	Not estimated	0.06 (0.00–0.90)	Very low ●○○○	It is uncertain whether high-flux membranes reduce β2-microglobulin-related carpal tunnel syndrome
β2-microglobulin complication: arthropathy	20 (1)	Not estimated	0.06 (0.00–0.90)	Very low ●○○○	It is uncertain whether high-flux membranes reduce β2-microglobulin-related arthropathy
Adverse events and safety	557 (13)	Not estimated	Not estimable	Very low ●○○○	It is uncertain whether high-flux membranes reduce adverse events in dialysis

All data derived from the 2013 Cochrane Review [56].

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significant benefit for high -flux membranes compared to low-flux membranes in relation to urea clearance or serum lipid levels. The data suggest that if 1000 individuals with ESKD were treated with high-flux HD there would be no reduction in all-cause mortality or hospitalization rates, but 15 fewer deaths might occur attributed to cardiovascular disease (CVD) causes.

Super-flux Membranes

At present there is limited clinical experience with the use of MCO membranes. Evidence is limited to nonrandomized studies.

The putative benefits outlined above are offset by concerns of albumin loss and back-filtration, and both need further evaluation. Albumin losses during a MCO HD session can approximate 3 g, but no significant change in serum albumin levels has been demonstrated and at present the clinical significance of these findings remains unclear [57, 58]. Similarly, in vitro studies have shown no increase in back-filtration, but this may become apparent with the increased clinical use of MCO membranes [20]. The efficacy of MCO membranes has been shown in small studies, with improved clearance rates of complement factor D (MW 24 000 D), α1-microglobulin (MW 33 000 D), and the chitinase-like protein YKL-40 (MW 40 000 D) compared to high-flux HD [27]. Dialysis with MCO membranes has been associated with reduced activation of the renin-angiotensin system and decreased expression of proinflammatory cytokines (TNF-a and IL-6) [59, 60].

These findings need further evaluation in prospective studies and correlation with clinical outcomes. An early example of such a study is REMOVAL-HD [61]. This is a prospective, investigator-led, open-label study which aims to address the safety, efficacy, and impact on patient-centered outcomes with the use of MCO membranes in 85 prevalent HD patients. The primary endpoint is the change in predialysis concentrations of serum albumin, with additional biochemical and patient-centered secondary endpoints. The outcomes will inform the design of future clinical trials which need to compare MCO membranes not only to high-flux membranes, but perhaps more importantly to convective therapies.

International Society Guidelines: High Versus Low Flux

Guideline	Year	Recommendation
KDOQI [62]	2015	• We recommend the use of biocompatible, either high- or low-flux, hemodialysis membranes for intermittent hemodialysis. High-flux dialyzers should be used preferentially, but if there are cost restraints, patients with diabetes mellitus, low albumin, and longer dialysis vintage should be prioritized.
Japanese Society for Dialysis Therapy Clinical Guideline [63]	2015	• High-performance membrane dialyzers should be used. These were defined in 2005 as a β2-microglobulin clearance of at least 10 ml/min and updated in 2013 to include albumin permeability and adsorption capability.
CARI-KHA [64]	2013	• We recommend that high-flux membranes be used to remove molecules such as β2-microglobulin because they have been shown to achieve lower serum levels. • We suggest there are possible survival benefits from high-flux membranes for some groups, such as those on dialysis for more than 3.7 years, those with a serum albumin below 40 g/l, and diabetics
Renal Association Clinical Practice Guidelines [65]	2011	• We suggest that hemodialyzers with synthetic and modified cellulose membranes should be used instead of unmodified cellulose membranes. • We suggest that high-flux dialyzers should be used instead of low-flux dialyzers to provide HD. Evidence of improved patient survival with the use of high-flux membranes is restricted to incident patients, who have lower serum albumin concentrations (<40 g/l) or have diabetes mellitus, and prevalent patients, who have been on HD for more than 3.7 years.
European Best Practice Guidelines [66]	2010 Update to the 2007 Guidelines	• Synthetic high-flux membranes should be used to delay long-term complications of hemodialysis therapy in patients at high risk (serum albumin < 40 g/l) • In view of underlying practical considerations and the observation of a reduction of an intermediate marker (β2-microglobulin), synthetic high-flux membranes should be recommended even in low-risk patients.

The Canadian Society of Nephrology Clinical Practice Guidelines published in 2006 provide no clear recommendation. KDIGO does not provide guideline on dialysis prescription or membranes.

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Discussion

The choice of dialysis membrane for HD remains a difficult question to answer based on hard evidence alone. Our preference reflects the default position in most higher-income countries, that of a high-flux, synthetic dialysis membrane. This is based on the putative benefits (improved biocompatibility, greater cardiovascular stability, and improved middle molecule clearance). The widespread uptake of synthetic membranes, along with reduced dialyzer reuse, have greatly reduced unit cost. Similarly, concerns about back-filtration and endotoxemia have been largely obviated by improvements in water quality. In countries where the availability of high-flux membranes remains limited, their use should be preferentially directed to patients with clinical characteristics that were associated with evidence of benefit, namely high cardiovascular risk. The choice between particular synthetic membranes is unlikely to be clinically significant, as any differences are probably small, and this has not been (or is likely to be) compared in head-to-head clinical trials. Finally, we await further clinical trial data pertaining to MCO membranes to assess any role in evidence-based clinical practice.

Evidence for HDF vs. HD

Much of the purported mortality benefit for HDF when compared to HD came from early observational studies [67–71]. These studies mostly compared postdilution HDF, albeit with variably defined effective convection volumes, to either low- or high-flux HD. The studies were heterogeneous in terms of the population studied as well as the type and quality of dialysis provided. As such these are particularly prone to the bias and confounding inherent to observational data, but the majority of these studies showed a mortality benefit for HDF when compared to conventional HD.

The four main RCTs comparing HDF to HD are summarized in Table 40.4 [37, 38, 72, 74]. These studies failed to provide clear answers, but in general did not demonstrate the mortality benefits hypothesized from the early observational trials. However, a consistent trend emerged from the secondary analyses, where a higher convection volume was associated with reduced all-cause and CVD mortality.

A 2015 Cochrane systematic review and meta-analysis included the three main RCTs (CONTRAST, ESHOL, and Turkish HDF), but also trials involving hemofiltration (HF) and acetate-free biofiltration [47] (Table 40.5). In general, the risk of bias was classified as high, resulting in a low level of confidence in the estimated treatment effects.

Convective dialysis probably did not decrease all-cause mortality (11 studies, 3396 participants, RR 0.87, 95% CI 0.72–1.05), although it probably reduced cardiovascular mortality (six studies, 2889 participants, RR 0.75, 95% CI 0.61–0.92). There was evidence that HDF reduced nonfatal cardiovascular mortality, infection related mortality or hospitalization. A reduction in dialysis-related hypotension with convective therapy was reported in one study (906 participants, RR 0.72, 95% CI 0.66–0.80). There was no significant benefit in terms of health-related quality of life, although the evidence was considered of very low quality. Convective therapies significantly reduced predialysis β2-microglobulin and increased dialysis dose (Kt/V urea), but results across the studies were heterogeneous and analysis limited to comparing HDF with HD yielded similar results. In absolute terms, it was suggested that convective therapies may prevent 25 cardiovascular deaths for every 1000 patients treated. In terms of surrogate outcomes there was a small reduction in predialysis β2-microglobulin levels (1813 participants, −5.55 mg/dl, 95% CI −9.11 to −1.98), however there was no evidence that HDF made any difference to predialysis blood pressure.

In a subsequent analysis, pooled individual participant data from the 4 major RCTs, which were designed to examine the effects of HDF on mortality endpoints, was used to study the effects of HDF on mortality outcomes in ESKD [73]. In the overall analysis HDF was associated with a proportional reduction in all-cause mortality by 14% (95% CI 1–24%) and cardiovascular mortality by 23% (95% CI 3–39%). There was no difference in subgroups, such as diabetics, but a closer scrutiny of convection volumes and mortality revealed that the benefit for HDF and all-cause mortality remained significant only in those patients who received convection volumes (>23 l/1.73 m per session [2]). Although this analysis has the advantage of a larger number of patients ($n = 2793$), the original trial issues remain, especially in regard to the differences in achieved convection volumes and HD type, and that these are non-randomized analyses. The major studies and meta-analyses all suggest a mortality benefit if higher convection volumes are achieved. However, the ability to "achieve" high convective volumes may simply reflect a well-functioning arterio-venous fistula, reasonably high blood flow rate, and the absence of major CVD disease. Therefore, patients achieving higher volumes may in fact be "better patients," biasing the high convective group to better outcomes.

Further trials are underway to further evaluate these questions. The CONVINCE trial, which is ongoing in Europe, is a randomized multicenter study involving 1800 patients comparing HDF to high-flux HD, with mortality as the primary endpoint (Netherlands Trial Registry, 7138). Careful attention is being paid to convection volumes, with a prespecified minimum of 23 l per session (body surface area [BSA] adjusted). In the meantime, the concept of "internal convection" has

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Table 40.4 Randomized controlled trials of HDF versus HD examining mortality as an endpoint (all involve postdilution HDF only).

Study	Comparators	N	Follow-up	Primary results	Subanalysis	Comments
2010, 27 Italian Centres (46).	LF HD, HF, or HDF	146 (70 HD, 36 HF, 40 HDF)	1.5 years	No difference HDF vs HD		Mortality not the primary endpoint Underpowered Randomization was between HD and convective therapy Randomization imbalances
CONTRAST, 2013, Netherlands (37)	LF HD vs. HDF	714	3 years	Mortality, no benefit	All-cause mortality benefit if UF volume > 21.95 L. No QoL benefit.	Benefit was in a post hoc analysis Not prespecified Included some twice-weekly dialysis
Turkish HDF, 2013 (74)	HF HD vs. HDF	782	2 years	Mortality, no benefit	CV and overall survival benefit if UF volume > 17.4 L	Benefit was in a post hoc analysis Not prespecified
ESHOL, Spain, 2013 (72)	HF HD vs. HDF (NB 8% low-flux HD in control arm)	906	3 years	Mortality benefit for HDF, all-cause HR 0.70; CV mortality HR 0.67		Prespecified requirement for UF volume >18 l Not clearly randomized, significant differences between groups that potentially influenced outcome 40% drop-outs
FRENCHIE, 2017, France (38)	HF HD vs. HDF	381, over age 65 years	120 days for primary outcomes, 2 years for secondary outcomes	Tolerance of dialysis sessions	No benefit in primary analysis Possibly some benefit at "session" level	Underpowered All-cause and cardiovascular mortality not different, including accounting for convective volume No difference in quality of life Some predilution HDF included

ACM, all-cause mortality; AVF, arteriovenous fistula; CRP, C-reactive protein; CV, cardiovascular; HD, hemodialysis; HDF, hemodiafiltration; HF, high-flux membrane dialyzer; LF, low-flux membrane dialyzer; QoL, quality of life.

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Table 40.5 Summary of findings: HDF (convective therapies) versus HD (diffusive therapies).

	Hemodiafiltration (convective modalities) therapy versus conventional hemodialysis (diffusive modalities): outcomes of interest				
Outcomes	**No. of participants (studies)**	**Absolute number of patients affected per 1000 patients treated for 1 year (95% CI)**	**Relative effect (95% CI)**	**Quality of the evidence (GRADE)**	**Conclusion**
All-cause mortality	3396(11)	26 fewer (56 fewer to 10 more)	0.87 (0.72–1.05)	Low ●●○○	HDF has little or no effect on all-cause mortality
Infection-related mortality[a]	2793 (4)	Two fewer (eight fewer to seven more)	0.94 (0.68–1.30)	Very low ●○○○	It is uncertain whether HDF reduces infection-related mortality
Cardiovascular mortality	2889 (6)	25 fewer (39 to 8 fewer)	0.75 (0.61–0.92)	Low ●●○○	HDF may reduce cardiovascular mortality
Nonfatal cardiovascular events	714 (1)	18 more (18 fewer to 64 more)	1.14 (0.86–1.50)	Very low ●○○○	It is uncertain whether HDF reduces non-fatal cardiovascular events
All hospital admissions	1688 (2)	Not estimable	1.21 (0.12–12.05)	Very low ●○○○	It is uncertain whether HDF reduces hospital admissions
Dialysis-related hypotension[b]	906 (1)	Not estimable[c]	0.72 (0.66–0.80)	Low ●●○○	HDF probably reduces the risk of dialysis hypotension
Quality of life	988(8)	Not estimable	Not estimable	Very low ●○○○	HDF/convective therapies have uncertain effects on quality of life
Change in dialysis therapy	2919 (5)	Four fewer (19 fewer to 40 more)	0.87 (0.30–2.52)	Low ●●○○	It is uncertain whether HDF results is a lower cross-over to another dialysis therapy
Residual renal function (RRF)	. . .(..)	..(. . .)	No studies	Absent	No studies found that evaluated the impact of HDF on residual renal function
β2-microglobulin complication: carpal tunnel syndrome	67(1)	Not estimable	Not estimable	Very low ●○○○	It is uncertain whether HDF reduces carpal tunnel syndrome incidence
Adverse events and safety	. . .(..)	..(. . .)	No studies	Absent	No studies found that evaluated the impact of HDF on adverse events and safety

The results where possible are derived from the Cochrane systematic review, Nistor et al. [47]; for some outcomes other systematic reviews are referenced and indicated where relevant.
[a] Metrics from Peters [73], 2016 individual pooled meta-analysis.
[b] Metric described is from Nistor et al. (Cochrane systematic review), but in addition three of four aggregate study meta-analyses also showed a benefit (consistent across all meta-analyses).
[c] Estimate using Maduell et al. [72], events per 1000 patient years suggest a possible reduction by 2585 events per 1000 patient dialysis years (3188–1875 events fewer).

re-emerged with the development of MCO membranes with high K_{uf} values, with high obligatory ultrafiltration and therefore back-filtration rates when used in HD mode. This has some similarities to HDF, but all of the volume transfer occurs within the dialyzer (as ultrafiltration and back-filtration). It has been argued that this approach may well provide many of the benefits of HDF without the need for additional equipment. This of course remains as yet unproven.

International Society Guidelines

It is important to note the HDF is not practiced in the United States and the uptake of HDF has been led by parts of Europe and Japan. Being a comparably novel therapy HDF has not been considered in the Canadian Society of Nephrology Clinical Practice, KDIGO, KDOQI, and KHA-CARI guidelines.

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Guideline	Year	Recommendation
Japanese Society for Dialysis Therapy Clinical Guideline [63]	2015	• HDF should enhance the removal of small proteins, reduce the production of inflammatory cytokines, and improve patients' prognoses. • HDF should be considered a therapy for nonspecific symptoms, including itching, joint pain, malaise, and poor appetite. Patients with dialysis hypotension should be considered for treatment with HD using a high-flux dialyzer and ultrapure dialysate.
Renal Association Clinical Practice Guidelines [65]	2011	• Both modalities are effective extracorporeal techniques for established renal failure but hemodiafiltration can provide higher rates of removal of small and middle molecules and may lower the risk of developing complications due to dialysis-related amyloidosis. • We suggest that high-flux HD using ultrapure water provides noninferior patient outcomes to hemodiafiltration.
European Best Practice Guidelines [75]	2007	• To exploit the high permeability of high-flux membranes, on-line HDF or HF should be considered. The exchange volumes should be as high as possible, with consideration of safety.

Conclusion

Despite the putative benefits of high-flux membranes such as improved middle molecule clearance and better biocompatibility, large RCT trails have failed to show a clear mortality benefit with the use of high-flux dialysis membranes. However, secondary analyses revealed a potential benefit in those with diabetes, low serum albumin, and longer dialysis vintage.

The increased adoption of high-flux membranes in the developed world has been driven in part by the presence of these clinical characteristics in many HD patients, as well as decreasing application of dialyzer reuse, which has resulted in a greater scale of manufacturing and decreased costs. Therefore, high-flux membranes are the default choice in most developed countries, but modified cellulosic membranes and low-flux membranes remain in use in many parts of the world and remain an appropriate choice in certain clinical situations.

The choice of dialysis modality remains a controversial topic, and the practice is highly variable across the world. The large treatment benefits of convective therapies seen in early observational studies were not confirmed by subsequent RCTs, although meta-analyses of intervention studies suggest there may be a benefit in relation to cardiovascular mortality and reducing the frequency of intradialytic hypotensive events. Moreover, the hypothesis-generating data suggesting higher convective volumes may be beneficial require further investigation in robust trials.

In summary, in modern dialysis units with ready availability of high-quality dialysis water, synthetic, high-flux dialysis membranes are now the accepted standard. The choice of dialysis modality remains less clear, and for most patients these therapies are likely to be of equivocal clinical benefit. Whilst we believe that HDF should not be routinely offered to all patients, it should be considered in patients with ongoing intradialytic instability and CVD, but only if adequate convection volumes can be achieved.

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Dialysis Dose and Adequacy for Hemodialysis

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Introduction

Dialysis is a laborious and expensive process for both patients and healthcare providers. Naturally, all stakeholders are interested in knowing "How much is enough?" The definition of "adequacy" – the necessary amount of dialysis – continues to evolve as our understanding of the impact of dialysis on patient quality of life and survival advances. The initial approach of Scribner and colleagues was to provide sufficient dialysis to alleviate the patient's uremic symptoms [2]. Then, with the observation that urea clearance was associated with survival, the focus shifted to delivering sufficient dialysis to achieve urea clearance targets using a normalized urea clearance formula: Kt/V. More recently, as the limitations of a "urea-centric" approach have become apparent, there has been growing interest in dialysis frequency and duration, and in the preservation of residual renal function. Finally, with an aging dialysis population, in which multimorbidity is the norm, an appreciation of patient goals and quality of life is helping to add nuance to patient–clinician discussions such that they extend beyond biochemical targets and mortality. Our approach in this chapter will be to consider dialysis adequacy as a multidimensional concept, incorporating a comprehensive assessment of the patient's needs, symptoms, and goals, and within which minimum urea-clearance standards provide a useful, but far from definitive, benchmark.

Definition of Dialysis Adequacy: Meets Patient Needs

It is important to distinguish between the narrow definition of adequacy as the "minimum acceptable urea clearance" and the broader concept of the "quantum and quality of dialysis (and associated therapies) that the patient requires." The two are not interchangeable. The former measure – in the form of the urea-reduction ratio (URR) or its normalized derivation (Kt/V) – retains importance as a useful and easily interpretable reference point. The latter recognizes that dialysis performs many functions – clearance of solutes (ranging from 60 to 60,000 daltons in mass) and control of sodium, water balance, and blood pressure – and forms part of a broader suite of therapies that also aim to maintain bone and mineral homeostasis and red blood cell production. No single measurement can combine all of these parameters. Moreover, urea-based adequacy does not consider the broader impacts of dialysis therapy on quality of life or the potential for dialysis-related complications such as access dysfunction or reduction in residual renal function. A true definition of adequacy therefore has to be multidimensional and flexible enough to accommodate differing patient characteristics and goals of therapy.

We propose a hierarchy of needs for dialysis recipients ranging from basic physiological survival to achievement of the best possible quality of life and longevity. Inspired by Maslow [3], this approach places the needs of the patient on

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Table 41.1 Assessment of level of evidence for intensity of hemodialysis therapy.

Treatment	Recommendation	Certainty of evidence	Strength of recommendation
Minimum dialysis hours	If <4 h per session is prescribed in a three times per week schedule, we suggest a comprehensive assessment of adequacy, including rates of volume removal, is performed regularly to avoid under-dialysis.	*Very low*	Weak
Increased dialysis hours	We suggest increasing dialysis hours for willing patients based on evidence suggesting improvements in quality of life, hyperphosphatemia, pill burden, and blood pressure. We suggest that longer hours may also be a useful way to treat patients with high ultrafiltration rate requirements, uncontrolled hypertension, poor phosphate control, and/or to improve some aspects of quality of life.	*High* (hyperphosphatemia, pill burden) *Moderate* (left ventricular hypertrophy) *Low* (quality of life, blood pressure control)	Weak
Dialysis frequency	We suggest that more frequent dialysis sessions (four to six per week) be offered to patients wishing to improve blood pressure, improve serum phosphate or reduce pill burden. It may also be recommended in patients with left ventricular hypertrophy and may have small benefits for some aspects of quality of life. Patients taking on this therapy should be advised of the possible risks of increased vascular access events and more rapid loss of residual renal function.	*Moderate to high* (hyperphosphotaemia, pill burden) *Moderate* (blood pressure, left ventricular hypertrophy) *Low* (quality of life, vascular access events and residual renal function)	Weak
Targeting urea clearance	We recommend achieving at least an spKt/V of 1.2. We suggest that this *not* be used as the primary measure of dialysis adequacy.	*Low*	Weak
Limiting volume Removal	We suggest targeting ultrafiltration rates below 10 ml/h/kg.	*Very low*	Weak
Incremental dialysis	We suggest that incremental dialysis be undertaken only within a structured program including regular reassessment of residual renal function and dialysis adequacy.	*Very low*	Weak

GRADE assessment of the certainty of the evidence [1]: High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different* is low. Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different* is moderate. Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different* is high. Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different* is very high. **Substantially different = a large enough difference that it might affect decision-making.*

a continuum (Figure 41.1). Adequacy of dialysis therapy is then judged from the patient perspective in relation to the degree to which these needs are met. This schema aims to encourage clinicians to go beyond urea clearance by focusing on biological parameters known to be associated with improved patient outcome and on a patient-centered concept of wellbeing. In general, "more" dialysis – whether increased frequency or duration – may be helpful for many patients in achieving higher-level needs but cannot be considered "adequate" without reference to the individual patient.

Epidemiology

The number of individuals receiving renal replacement therapy is growing steadily, it is expected to reach 3.8 million in 2020 and rise to 5.4 million by 2030 [4]. This burden is not distributed equally and rates of dialysis and transplant uptake vary dramatically around the globe, from over 2000 per million population in Japan to as low as 2.8 per million population in Rwanda [5]. These figures are also likely to hide as many as 9.7 million individuals with ESKD who are unable to receive renal replacement therapy due to resource limitations [4]. For those fortunate enough to have access to dialysis, hemodialysis is the dominant modality, with the proportion of dialysis delivered as hemodialysis estimated to be 89% in 2013 [6]. This also varies from region to region, with the proportion on hemodialysis being as low as 20.6% in Hong Kong and greater than 99% in some countries [7].

Three sessions per week is near universal in high-income countries, with less than 5% of patients receiving

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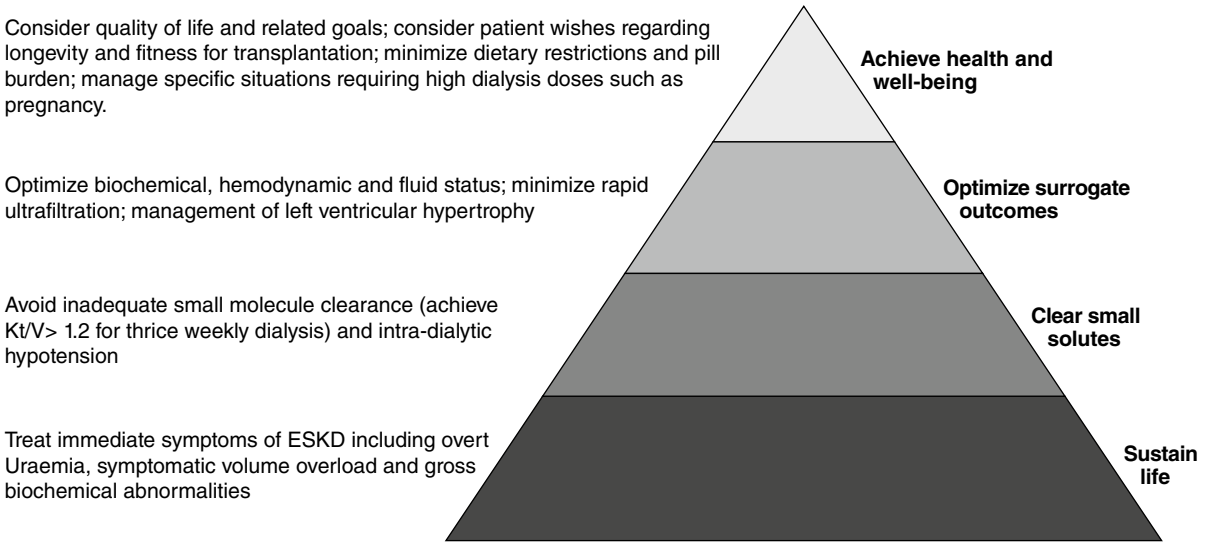

Figure 41.1 Hierarchy of needs for the hemodialysis patient.

two or fewer sessions per week [8]. More frequent dialysis is also uncommon, although its prevalence varies from 14% in Sweden to <1% in the United States, Japan, and France [8]. In contrast, in 2011 up to 26% of patients in China were dialyzing twice weekly [9]. Although accurate data is lacking, twice-weekly dialysis is believed to be common practice in many low- and middle-income countries. Average session length also varies globally, with the mean value in most countries lying between 3.5 and 4 hours [8–10]. Other differences in dialysis delivery should be noted, with high-income countries typically providing high-flux dialysis with no dialyzer reuse. In contrast, low-flux dialysis and dialyzer reuse is common in many middle-income countries [11]. This is likely to contribute to poorer outcomes in these countries, although the relative impact of these practices on morbidity is not well described.

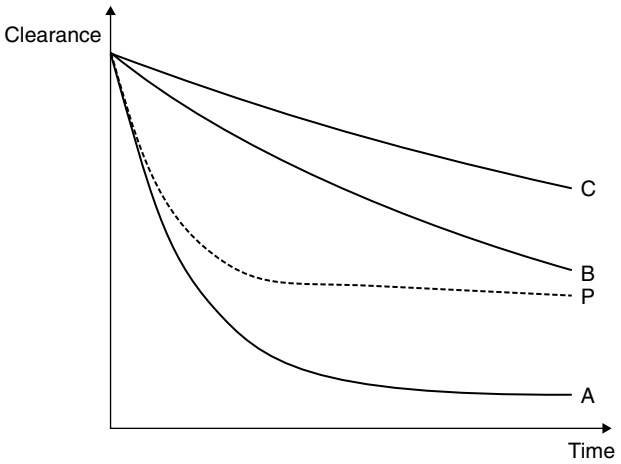

Figure 41.2 Clearance vs. time curves for solutes during a single dialysis session. A represents small solute clearance (e.g. urea). B and C represent larger solutes of varying weight (e.g. middle molecules). P (dashed line) represents clearance of a sequestered small solute (e.g. phosphate).

Pathophysiology

In high-income countries, where the use of high-efficiency and high-flux dialyzers is now standard, the question of dialysis adequacy is essentially a discussion of the relationship of solute and water clearance with dialysis time and frequency. Detailed discussion of dialyzer characteristics and the impact of blood and dialysate flow rates can be found elsewhere [12] and is beyond the scope of this chapter.

Figure 41.2 demonstrates the relationship between rate of solute clearance on dialysis and dialysis session time. It illustrates the three concepts central to understanding the prescription of dialysis time and frequency:

1) Solute clearance is greatest at the start of dialysis when the concentration gradients are highest [12]. For this reason, more frequent dialysis sessions (e.g. six vs. three times per week) allow more time on the steepest part of the removal curve, increasing small solute clearance even if total dialysis time remains the same [13].
2) As solute size increases, the rate of diffusion decreases. Thus, as solute size increases the concentration gradient

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between blood and dialysate changes less rapidly, leading to greater "gain" in clearance from longer sessions. As a result, total dialysis time is more important than frequency for middle-molecule clearances.

3) "Sequestered" solutes display a biphasic clearance. Initially, the rate of clearance from the first compartment (blood or extracellular space) may decline relatively rapidly as the concentration gradient diminishes. This is followed by the mobilization of solute from secondary compartments which maintains the concentration gradient between blood and dialysate, and leads to a second phase of clearance in which the rate of clearance is maintained over the later hours of the dialysis session. The classic example of this phenomenon is phosphate. Up to four compartments have been proposed to adequately model intradialytic phosphate clearance [14, 15]. In all models, the initial clearance from the blood compartment is rapid, but beginning in the second hour of dialysis the rate of clearance plateaus as sequestered solute is mobilized from less accessible compartments. The result is that phosphate clearance can be improved with both increased session frequency (maximizing the time with rapid clearance) and increasing dialysis time (as clearance does not diminish over longer dialysis sessions).

Water "clearance" – i.e. ultrafiltration – is distinct from other parameters. The rate of ultrafiltration required to maintain euvolemia is determined by fluid intake, urine output, and the interaction between dialysis frequency and session length. More frequent sessions minimize fluctuations in volume status and longer sessions permit slower rates of ultrafiltration. Both large intradialytic weight gain and rapid ultrafiltration are associated with increased morbidity and mortality [16, 17]. Increasing session length (if frequency remains the same) tends to reduce the rate of ultrafiltration. Increasing session frequency (if total dialysis hours remains the same) may reduce the size of intradialytic weight gain (Figure 41.3).

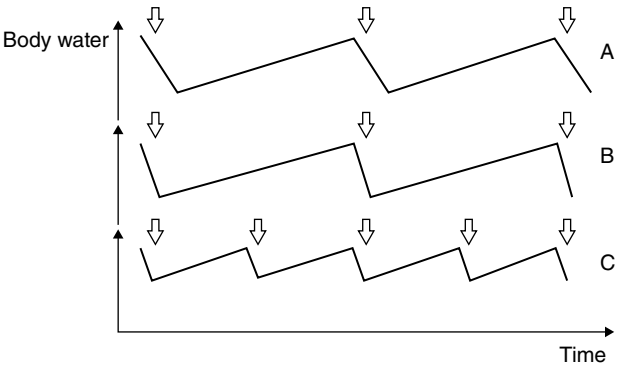

Figure 41.3 Pattern of volume changes with different dialysis schedules. (A) Thrice weekly 8 hours, (B) thrice weekly 4 hours, (C) frequent dialysis 2.4 hours × five sessions per week. Arrows indicate dialysis sessions.

Diagnosis

Dialysis therapy must be tailored to fit the patient. This requires a thorough exploration of the patient's symptoms, nutritional status, cardiovascular risk, and fluid status, bone, and metabolic health and, equally important, their goals, functional limitations and supports. Hence, assessment of adequacy requires a thorough clinical assessment *and* a frank discussion about patient expectations of treatment. We present here an indication of the information required to facilitate an adequacy assessment. An introduction to principles of urea kinetic modeling (UKM) is also provided as this remains a useful component of the adequacy assessment.

Comprehensive Clinical Assessment

The comprehensive clinical assessment should include the following:

1) Symptoms
   a) Uremic symptoms, such as nausea, poor appetite, pruritis, and restless leg syndrome.
   b) Symptoms of over- or under-hydration, including dyspnea, edema, thirst, and orthostatic dizziness.
   c) Adverse symptoms of dialysis, including cramps on dialysis and post-dialysis fatigue.
   d) Common comorbid symptoms, such as pain, disturbed sleep, and limitations to mobility
2) Physical examination
   a) Volume status and blood pressure
   b) Access assessment
3) Dialysis parameters
   a) Ideal body weight and interdialytic weight gain
   b) Pre- and postdialysis blood pressure
   c) Kt/V urea
4) Laboratory parameters
   a) Small solute clearance: urea, creatinine, potassium
   b) Anemia: hemoglobin, ferritin, and iron-binding capacity
   c) Volume status: sodium
   d) Nutrition: albumin, bicarbonate
   e) Bone and mineral disorder: phosphate, calcium, parathyroid hormone, alkaline phosphatase

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5) Medication review
   a) Avoid overprescribing and consider pill burden
6) Cardiovascular assessment
   a) Consider screening for left ventricular hypertrophy
7) Functional status
   a) Multiple standardized measures of function and frailty exist, including the Karnovsky Performance Score or Clinical Frailty Scale [18]. Simple tests such as the Timed Up and Go may also be effective screening tools [13].
8) Social environment and supports
   a) Understand the patient's social environment and the demands on their time that may conflict with dialysis (e.g. employment, training, caregiver). Consider the needs of the patient's caregivers. Patient and caregiver responsibilities may heavily influence the choice of dialysis frequency and session length.
9) Goals and expectations
   a) What does the patient wish to achieve with dialysis therapy? What are their goals and how do they prioritize those goals? For instance, do they wish to receive a kidney transplant? Is dialysis aimed to extend life expectancy? To maximize their function? To spend time with family or friends? To enable travel and flexibility? Are their (and their family's or carer's) expectations of hemodialysis realistic?

Urea Kinetic Modeling

UKM refers to mathematical modeling that approximates the observed clearance of urea during one or more dialysis sessions by relating basic patient characteristics, such as urea generation and total body water, with parameters of dialysis therapy, such as time, dialysate flow rate, and dialyzer urea clearance. The field developed with the understanding that simply targeting low blood urea levels did not always result in better patient outcomes as low blood urea levels often reflected poor nutrition rather than adequate dialysis [19]. The details of modern UKM are beyond the scope of this chapter and quickly exhaust the patience of many physicians. Fortunately, as many excellent resources exist for those wanting a deeper understanding of the topic [7], we will focus attention mainly on the key concept of Kt/V_{urea} and the evidence supporting its current role in dialysis prescription.

Kt/V

The most commonly used marker of small molecule clearance is Kt/V, where:

K = dialyzer urea clearance (ml/min) (a function of dialyzer surface area and permeability, and blood and dialysate flow rates)

t = dialysis time (min) (hence, Kt represents the volume (ml) of plasma cleared of urea during the dialysis session)

V = postdialysis volume of distribution of urea (ml) (equivalent to total body water)

The advantage of this formula is that it is not dependent on absolute levels of blood urea, and therefore is independent of nutrition. Rather, as dialyzer urea clearance is a general surrogate for dialytic clearance of many small molecules, it represents a generalizable dialysis parameter. In choosing a dialyzer with known characteristics, dialysate and blood flow rates and treatment time, one can specify a desired Kt/V. UKM computer programs are available that facilitate this calculation.

In practice, owing to access recirculation and the error involved in the multiple assumptions underlying the model, prescribed Kt/V often differs substantially from the actual "delivered" Kt/V. Delivered Kt/V is therefore the key value to aid in adequacy assessments. Values below target should prompt titration of the variable parameters (for instance an increase in dialyzer size or session time) to increase clearance (consideration of access recirculation may also be warranted), with improvement confirmed by subsequent testing of the delivered Kt/V.

Single-pool *Kt/V*

In its simplest form, Kt/V is calculated assuming that urea is distributed evenly through one fluid compartment and is known as a single pool, or spKt/V. The most widely used equation to calculate delivered spKt/V is that of Daugirdas [12]:

$$\mathrm{sp}Kt/V = -\ln\left(U_{\mathrm{post}}/U_{\mathrm{pre}} - 0.008\times t\right) + \left(4 - 3.5\times U_{\mathrm{post}}/U_{\mathrm{pre}}\right) \times V_{\mathrm{uf}}/\mathrm{weight}$$

where U_{post}/U_{pre} is the ratio of postdialysis to predialysis urea, t is the treatment time in hours, Vuf is the ultrafiltration volume, weight is bodyweight in kilograms, and ln is the natural logarithm.

This equation has the advantage of including ultrafiltration volume (hence convective urea clearance) and intradialytic urea generation. It is validated between Kt/V values of 0.7 and 2.1 [20].

Equilibrated *Kt/V*

The assumption of a single pool of urea is an oversimplification, as demonstrated by the fact that blood urea levels rapidly rebound after dialysis is completed. This means that spKt/V overestimates urea clearance. To account for this, equilibrated, or eKt/V can be calculated, either by taking a second urea sample 35 minutes after the

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completion of the dialysis session or by modifying spKt/V using a conversion equation shown to reliably approximate measured eKt/V [8]:

$$\mathrm{e}Kt/V = \mathrm{sp}Kt/V \times \left(t/t+35\right)$$

where t is dialysis time in minutes.

Standard *Kt/V*

Standard Kt/V (stdKt/V) was devised to permit comparisons between dialysis regimens of different frequency or with peritoneal dialysis. The modeling equations utilize the pre- and postdialysis blood urea, and dialysis and patient parameters over a 1-week period to estimate the urea clearance required to maintain those values in a steady state. A number of different modeling equations are available to estimate stdKt/V, some of which incorporate residual renal function and/or convective urea clearance [9, 10]. StdKt/V is most important if patients receive incremental hemodialysis (less than three times per week) as an aid to the up-titration of dialysis in line with loss of residual renal function.

Urea Reduction Ratio

URR is the simple ratio of the change in urea during dialysis to the predialysis urea level (conventionally expressed as a percentage):

$$\mathrm{URR} = \left(U_{\mathrm{pre}} - U_{\mathrm{post}}\right)/U_{\mathrm{pre}} \times 100$$

(This is sometimes written as the equivalent formula URR = 1 – ($U_{\mathrm{post}}/U_{\mathrm{pre}}$).)

URR is related exponentially to Kt/V such that, as Kt/V rises, further large increases result in only small changes in URR. For example moving Kt/V from 1.5 to 2.0 results in an increase in URR from 73% to 82%. While simpler, it does not account for urea clearance due to ultrafiltration, nor the generation of urea during the dialysis session. Despite these limitations, observational evidence suggests that URR predicts outcomes similarly to Kt/V and it remains a part of current treatment guidelines [21].

Caveats in Interpreting *Kt/V*

It is important to be aware of the risk of under-dosing by Kt/V in smaller patients, such as women and children, in whom the lower value of V may lead to the prescription of shorter dialysis sessions, smaller dialyzers, or slower blood or dialysate flows. The risks of this were emphasized by in the HEMO trial, in which women randomized to the "standard" Kt/V target had a higher mortality than those in the "high" Kt/V arm [22]. Conversely, patients with higher body fat, in whom V overestimates total body water will tend to require increased dialysis dosing to achieve target Kt/V. This has been speculated to contribute to the observed survival benefits of higher body fat in hemodialysis recipients [23].

Conductivity-based measures of Kt/V are now available on many dialysis machines. These operate by manipulating the sodium concentration of the inflowing dialysate in a controlled fashion and measuring the resulting differences in electrical conductivity between the inflowing and outflowing dialysate. This provides a ready measure of small molecule clearance that can be used as a surrogate for urea clearance and therefore Kt/V. While correlated with urea-based Kt/V, conductivity measures tend to underestimate Kt/V and within-patient variation may be high [24, 25]. Given these limitations and the lack the clear observational and randomized controlled trial data to support their use, conductivity measures should be supplemented by periodic urea-based estimates of delivered Kt/V.

Assessment of Residual Kidney Function

Residual kidney function (RKF) is associated with quality of life [26] and lower mortality [27, 28]. This is thought to be due to the continuous provision of both small and middle molecular clearance and the beneficial impact on mineral metabolism and smoothing of fluid status fluctuations. Assessment of RKF typically plays little part in the prescription of hemodialysis, with most patients commencing a three times per week schedule from the initiation of dialysis [29]. This approach, essentially treating RKF as "bonus" clearance that does not require further consideration, has been challenged due to the observation that more frequent dialysis may be associated with more rapid loss of renal function [30].

Measurement of RKF is hampered by the fact that small solutes fluctuate with each dialysis session, that glomerular filtration is not constant in the interdialytic interval [31], and that extrarenal clearance (e.g. gastrointestinal) is not well-understood or quantified [32]. Optimal measurement demands urine collection over the entire (e.g. 44-hour) interdialytic interval. Creatinine-based measurements tend to overestimate RKF owing to tubular creatinine secretion, whereas urea-based measures underestimate it due to passive reabsorption of urea in the distal tubules.

Multiple methods of assessing RKF exist. Residual urea clearance (K_{ru}) can be reasonably approximated in a patient performing three sessions per week using a 24-hour urine collection commencing the day prior to a mid-week dialysis session using the following formula:

$$K_{\mathrm{ru}} = \frac{U_{\mathrm{urine}}}{U_{\mathrm{serum}} \times 0.9} \times \text{urine flow rate}\left(\mathrm{ml/min}\right)$$

where 0.9 is a factor that adjusts the predialysis serum urea value to approximate the mid-week mean [31].

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An alternative is to estimate RKF by the average of K_{ru} and K_{rCr} (residual creatinine clearance), utilizing the fact that the former underestimates and latter overestimates true RKF. Some authors, however, recommend relying only on K_{ru} on the understanding that the underestimate results in an assumed "buffer" providing a modicum of safety from under dialysis [33].

Prognosis

Longer treatment times are associated with longer life expectancy. Using data from 12 countries, Tentori et al. demonstrated an average reduction in risk of mortality of 6% for every 30 minute increase in session length [34]. The reasons for this finding are not clearly understood. Higher Kt/V may be one factor, but owing to the kinetics of small solute clearance the increase in Kt/V with increased time steadily diminishes as session length increases (c.f. Figure 41.2). Indeed, the observed mortality relationship is lost above Kt/V of approximately 1.3 [35]. Other factors are clearly important.

Observational studies have shown a dose-related increase in mortality with increasing ultrafiltration rates [16, 17]. For example, a 22% increase in mortality in those with rates >10 ml/h/kg (vs. ≤10 ml/h/kg) and a further 31% increase in those with rates >13 ml/h/kg (vs. 10–13 ml/h/kg) [36]. The benefits of slower ultrafiltration are hypothesized to stem from lower incidence of intradialytic hypotension and the myocardial strain associated with dialysis [37]. Other potential benefits include preservation of RKF, which in itself is clearly associated with improved prognosis [28]. Furthermore, increased session length is associated with lower phosphate levels, which are consistently associated with lower mortality [38].

Other prognostic factors that might impact on adequacy assessment are hypertension and fluid overload. The association with fluid overload is consistent. Studies utilizing bioimpedance spectroscopy have shown fluid overload (both pre- and postdialysis) to be positively associated with mortality [39, 40]. The relationship between hypertension and mortality in the ESKD population is the subject of substantial debate. Observational studies suggest a U-shaped association, with marked increases in mortality with low (<130/70 mmHg) predialysis systolic and diastolic blood pressure, and less pronounced increases with systolic blood pressure >180 mmHg [41]. Confounding by cardiovascular disease is likely to contribute to this phenomenon. Interdialytic blood pressure is poorly correlated with predialysis values and may display a different (more traditional) relationship with mortality. This uncertainty aside, current practice remains to treat hypertension in hemodialysis patients and the beneficial impact of improved fluid control and increased dialysis frequency or duration on blood pressure (see below) should be included in assessment of dialysis adequacy.

Treatment

Evidence Behind the Current Guidelines

Current guidelines are derived from the results of two pivotal clinical trials: the National Co-operative Dialysis Study (NCDS) and the HEMO study (Box 41.1). The NCDS, published in 1981, sought to determine if lower time-averaged urea levels were superior to higher, and if 3 vs. 4.5 hours was superior [42]. The time averaged urea (TAC_{urea}) targets of 50 vs. 100 mg/dl (18 vs. 36 mmol/l) were approximately equivalent to predialysis urea levels of 70 and 120 mg/dl (25 vs. 43 mmol/l). Patients with residual creatinine clearance greater than 3 ml/min were excluded. The study was terminated early as participants in the high TAC_{urea} arm had a higher incidence of death, withdrawal from dialysis, and hospitalization. There were no significant differences between those assigned to 3 vs. 4.5 hours of dialysis. Subsequent criticism of the study focused on the fact that the use of urea concentration as the treatment target was likely to have led to participants with a higher protein intake to be prescribed higher dialytic clearance compared to participants in the same arm of the study with a lower protein intake. This resulted in divergent outcomes depending on nutritional status, with little between-group separation in delivered dialysis clearance in those with low protein intake and a large difference for those with a higher protein intake. To account for this, Gotch and Sargent developed Kt/V as a way to measure dialysis dose independently of protein catabolic rate [19]. Their reanalysis of the NCDS data established that good clinical outcomes were associated with $Kt/V > 0.8$. Further work increased this cut-off value to 1.0 and observational data suggested that outcomes continued to improve above this value [43, 44]. The resulting uncertainty as to the optimal dose (based on Kt/V) led to the development of the HEMO study.

The HEMO study, published in 2002, randomized participants in a factorial design to high or low flux membrane and a higher or lower dialysis dose by Kt/V [22]. The low and high Kt/V arms achieved an spKt/V of 1.32 ± 0.09 (eKt/V 1.16 ± 0.08) and 1.71 ± 0.11 (eKt/V 1.53 ± 0.09), respectively; approximately equal to a URR of 65–75%. The study found no difference in mortality with dialysis dose (or flux): relative risk (high vs. standard) 0.96 (0.84–1.10, $P = 0.53$) and, for high vs. low flux, 0.92 (0.81–1.05, $P = 0.23$). Nor were there differences in hospital admissions. The

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higher Kt/V was achieved not only by increasing treatment time (average 219 vs. 190 minutes) but also by a 20% increase in blood flow rates and small increases in dialyzer size and dialysate flow rates. As such, the results cannot be generalized to include increasing Kt/V while holding dialyzer size and flow rates the same, either by increased dialysis time or by increasing standardized Kt/V by increasing dialysis frequency. During screening, patients had to be able to achieve an eKt/V of at least 1.30 during a 4.5 hour session in order to enter the study. Due to the difficulty of achieving high Kt/V in large patients, only 3% of participants were greater than 100 kg, thus also limiting the generalizability to larger patients. The study also excluded those with a residual urea clearance of greater than 1.5 ml/min per 35 l urea volume and 67% of participants were anuric. Compared to the standard-dose group, women in the high-dose group had a 19% lower relative risk of mortality, but men had a 16% higher relative risk of mortality.[1] Differences in body size and composition have been postulated to explain these findings and no further randomized studies are available to clarify them.

Increased Dialysis Frequency and Session Length

The "un-physiological" nature of thrice weekly intermittent hemodialysis has always been recognized and is elegantly demonstrated by the clear peak in mortality at the end of the long 2-day break in patients on standard thrice weekly dialysis routines [45]. Yet, the randomized trials of different urea clearance targets have been limited to thrice weekly dialysis with session times reaching a maximum of 4.5 hours (the mean value in the high dose HEMO arm was 4 hours, 9 minutes) [22, 42].

Observational evidence clearly favors longer sessions. Dialysis times ≥4.5 hours and $Kt/V \geq 1.3$ are associated with lower mortality [46]. Saran et al. demonstrated that (after adjustment for confounders including Kt/V measured urea clearance) each 30 minute increase in dialysis time was associated with a 7% relative risk reduction in all-cause mortality [47]. They also observed a synergistic association between Kt/V and dialysis time, where the mortality benefit of increased Kt/V was amplified at longer dialysis times, although this interaction has not been observed in all studies [46]. A meta-analysis of observational studies concluded that, compared with conventional hemodialysis, home nocturnal dialysis (hazard ratio [HR] 0.46, 95% CI 0.38–0.55), in-center nocturnal dialysis (HR 0.73, 95% CI 0.60–0.90), and home short daily dialysis (HR 0.54, 95% CI 0.31–0.95) all provide substantial mortality benefits [48]. The observed benefits of longer dialysis times may be in part due to slower ultrafiltration, with ultrafiltration rates <10 ml/kg/h being associated with lower mortality and lower cardiovascular morbidity, presumably due in part to the deleterious effects of intradialytic hypotension [16, 36, 47]. Despite this, the possibility of residual confounding limits any conclusions regarding mortality based on observational data. Indeed, concern has been raised regarding frequent short daily in-center dialysis with an increased mortality seen in a propensity matched cohort study (HR 1.6, 95% CI 1.1–2.3) [49].

Between 2007 and 2017, a series of small, but important randomized trials of more frequent or extended hours dialysis (the findings of which are summarized in Table 41.2) have been published. The first three trials focused on dialysis frequency and compared five or six times per week to thrice weekly hemodialysis, with the Frequent Hemodialysis Network (FHN) Daily study utilizing short dialysis sessions (1.5–2.75 hours) [50] and the Culleton et al. [51] and the FHN Nocturnal [52] studies utilizing sessions of at least 6 hours in length. In contrast, the ACTIVE Dialysis trial compared total weekly dialysis hours of ≥24 hours (mostly delivered in three 8-hour sessions) to a standard regimen of ≤18 hours per week (delivered in three sessions) [53]. All studies were small (totaling 584 participants) and lasted no longer than 12 months. All demonstrated a reduction in left ventricular mass, although this was significant only in the Culleton et al. and FHN Daily studies. There were clear reductions in two important surrogate endpoints: serum phosphate and systolic blood pressure, with associated reductions in the need for phosphate binders and antihypertensives. Quality of life measurements were also stable or improved in the frequent or extended hours dialysis groups [50–52, 54].

Long term follow-up data is available for the FHN trials and provides conflicting signals. After a median follow-up of 3.6 years, the risk for mortality in the frequent in-center hemodialysis group of the FHN Daily trial was almost half that in the conventional group (HR 0.54 [95% CI 0.31 to 0.93, $P = 0.024$]) [55]. In contrast, in long-term follow-up of the 87 participants of the FHN Nocturnal trial, an increased risk of mortality was observed in the frequent home dialysis group (HR 3.88 [95% CI 1.27–11.79, $P = 0.01$]) [56]. Both results, the latter in particular, should be interpreted with caution owing to the small number of events in each arm. The potential harms of frequent dialysis could include an increase in dialysis-related myocardial stunning [37] or cerebral ischemia (which is not simply predictable from blood pressure and is associated with cognitive dysfunction) [57]. As such, the long-term impact of frequent dialysis remains unclear.

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Table 41.2 Summary of findings: individual randomized trials of increased dialysis time or frequency.

Outcomes	Culleton et al. *N* = 51 6 m	FHN Nocturnal *N* = 87 12 m	FHN Daily *N* = 245 12 m	ACTIVE Dialysis *N* = 200 12 m	Certainty of evidence (GRADE)	Conclusion
	5-6×/week ≥6 h/session (home, nocturnal) vs. 3×/week sp*Kt/V* ≥ 1.2 (in-center)	6×/week ≥6 h/session (home) vs. 3×/week <5 h e*Kt/V* ≥ 1.1 (home)	5-6×/week 1.5–2.75 h/session (in-center) vs. 3×/week e*Kt/V* ≥ 1.1 (in-center)	≥24 h/week (3×/week, 8 h) (in-center, home) vs. ≤18 h/week (3×/week, 4–5 h) (in-center, home)		
Mortality	–	HR 3.88 (1.27, 11.79)	HR 0.54 (0.31, 0.93)	–	Low ●○○○	Widely divergent estimates of the mortality impact of frequent nocturnal and daily dialysis do not permit definitive answer
Left ventricular mass index (g/m^2)	−8.1 (−16.2, −0.1)	−4.4 (−10.8, 2.1)	−7.1 (−12.0, −2.2)	−6.0 (−14.8, 2.7)[2]	Moderate ●●○○	More frequent or extended dialysis may reduce left ventricular mass index
Phosphate (mmol/l)	−0.48 (−0.81, −0.16)	−0.45 (−0.68, −0.23)	−0.18 (−0.29, −0.07)	−0.25 (−0.35, −0.16)	High ●●●●	Frequent or extended dialysis reduces phosphate
Systolic blood pressure (mmHg)	−11 (−24, 2)	−9.7[3] (−16.9, −2.5)	−10.1 (−14.3, −6.0)	−2.9 (−6.8, 1.1)	Moderate ●●○○	Frequent dialysis lowers blood pressure, the impact of extended dialysis is not clear and may be affected by changes in antihypertensive agents
Parathyroid hormone (pmol/l)	−8.9 vs. +1.6[4]	−4.0 (−6.7, 0.4)	2.8 (−0.3, 6.8)	−1.3 (−14.4, 11.9)	High ●●●●	Frequent or extended dialysis is unlikely to change parathyroid hormone
Calcium (mmol/l)	0.025 (−0.075, 0.100)	No change	No change	0.05 (0.01, 0.09)	High ●●●●	Frequent or extended dialysis does not have an important effect on calcium
Physical quality of life (score range 0–100)	1.5 (−2.2, 5.2)	0.6 (−3.4, 4.7)	3.2 (1.0, 5.4)	2.3 (0.5, 4.1)	Low ●○○○	Physical and mental quality of life may improve with frequent daily or extended dialysis; neither appear to be affected by frequent nocturnal dialysis
Mental quality of life (score range 0–100)	2.5 (−3.0, 7.9)		3.7 ± 0.9 vs. 0.2 ± 1.0; $P < 0.01$	2.5 (0.4, 4.7)	Low ●○○○	

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EQ-5D health utility	0.05 (−0.07, 0.17)			0.04 (−0.03, 0.11)	Low ●○○○	Increased dialysis does not improve health utility
Other quality of life	Improved effects of kidney disease (8.6 /100 [2.0, 15.2]) and burden of kidney disease (9.4 /100 [1.3, 17.5]); no change in symptoms/problems, sleep	No change in Beck depression inventory	No change in Beck depression inventory	Kidney Disease Composite Score (3.48 [1.44, 5.51]; $P < 0.001$)	–	
Medication use	Reduction or cessation of antihypertensives and (16/26 vs. 3/25; $P < 0.001$) phosphate binders (19/26 vs. 3/25; $P < 0.001$) more common	Fewer antihypertensives (−0.97 vs. 0.26; $P < 0.001$); fewer phosphate binders (no binders 73% vs. 8%; $P < 0.001$)	Fewer antihypertensives (−0.87 vs. −0.23; $P < 0.001$); lower equivalent dose of phosphate binders (−1.35 g/day [−2.50, −0.20])	Fewer phosphate binders (−0.83 [−1.61, −0.04]; $P = 0.04$); fewer antihypertensives (−0.29 [−0.53, −0.06]; $P = 0.01$)	High ●●●●	Frequent or extended hours dialysis reduces the need for antihypertensives and phosphate binders
Incident anuria		Trend to increase (67% vs. 36%; NS)	No change (53% vs. 48%; NS)		Low ●○○○	Loss of residual renal function may be more rapid with frequent dialysis
Adverse events	No difference in vascular access complications	Less intradialytic hypotension (3.1% vs. 9.5% of sessions; $P < 0.001$); trend toward more vascular access complications (HR 1.88 [0.97, 3.64])	No difference in hospitalizations or access interventions	No difference in access interventions or adverse events	Moderate ●●○○	An increase in vascular access events with frequent dialysis cannot be excluded

CI, confidence interval. GRADE assessment of the certainty of the evidence [1]: High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different* is low. Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different* is moderate. Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different* is high. Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different* is very high. **Substantially different = a large enough difference that it might affect decision-making*.

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The FHN Daily trial identified a number of negative effects of frequent dialysis. A nonsignificant increase in the number of vascular access interventions (HR 1.35 [95% CI 0.84–2.18, $P = 0.22$]) was noted, which was significant when time to first access intervention was examined (HR 1.71, 95%CI 1.08–2.73) [50]. A similarly significant increase in the risk of vascular access failure or intervention was seen in the FHN Nocturnal trial (HR 1.88 [95% CI 0.97–3.64, $P = 0.06$]) [52]. No significant differences in vascular access complications were noted in the Culleton et al. or ACTIVE trials [51, 53]. The impact of frequent dialysis on residual renal function was examined in both the FHN Daily and Nocturnal trials with an increase in incident anuria (i.e. loss of residual renal function) seen in the Nocturnal trial (relative risk [RR] 1.83, $P = 0.06$) but not in the Daily trial (RR 1.11, $P = 0.99$) [30]. Caregiver burden also emerged as a consideration in the FHN Nocturnal trial, where a trend toward increased perceived caregiver burden (as measured by the Cousineau scale) was identified (6.1 [95% CI −0.8 to +13.1, $P = 0.08$]). No such trend was evident in the FHN Daily trial [58].

Incremental Dialysis

There is growing interest in a gradual approach to dialysis initiation. This is informed by the knowledge that RKF typically remains substantial when dialysis is initiated and the obvious corollary that patients might therefore require less dialysis in the early months and years after commencing dialysis. Moreover, observational studies suggest that twice-weekly dialysis is associated with preservation of RKF [59]. The hypothesis that more dialysis accelerates loss of RKF was strengthened by the results of the FHN trials in which participants assigned to frequent dialysis suffered a greater decline in RKF and/or urine volume [30]. When these observations are coupled to the well-described association between RKF and survival in hemodialysis patients [27, 28], the argument for incremental exposure to dialysis appears compelling.

However, the observational evidence (including both prospective and retrospective studies) has proven conflicting. While similar survival between twice weekly/incremental dialysis and standard thrice weekly has been demonstrated in multiple studies [60–63], residual confounding may explain many of these findings and an increase in mortality has also been observed in other studies. For example, a prospective study involving 685 participants found a fourfold increase in mortality in adjusted analysis among patients with RKF undergoing twice weekly dialysis compared to those undergoing three-times weekly dialysis (HR 4.20 [95% CI 1.02–17.32, $P = 0.04$]) [64]. A larger retrospective study in the United States compared 351 incremental dialysis patients to 8068 matched patients (including matching by RKF) and found equivalent mortality in those with baseline RKF > 3.0 ml/min/1.73 m^2 (HR 0.99, 95% CI 0.76–1.28) but increased mortality in those with ≤3.0 ml/min/1.73 m^2 (HR 1.61, 95% CI 1.07–2.44) [65]. These studies highlight the potential risks involved with incremental dialysis, especially in patients with minimal residual renal function (e.g. urea clearance <3 ml/min/1.73m^2, urine volume <600 ml/day) and emphasize that a well-structured program with clear patient understanding is necessary for such a program to be implemented. Future randomized controlled trials are required to ascertain the benefits and safety of this approach.

Summary of Findings

The evidence base for dialysis dosing is limited, with no high-quality systematic reviews published that include all

Box 41.1 Current Guideline Positions

The most recent Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines for Hemodialysis Adequacy: 2015 Update [21] incorporate the long-term follow-up data from the FHN studies and the findings of the ACTIVE Dialysis trial.

KDOQI guidelines recommend a per session sp*Kt/V* target of 1.4 with a minimum delivered *Kt/V* of 1.2. For patients on more or less frequent dialysis the recommended target std*Kt/V* is 2.3 with a delivered std*Kt/V* of 2.1 (using an equation that considers ultrafiltration and residual renal function). A minimum time per session of 3 hours is recommended for those with minimal residual renal function. They also suggest that dialysis dose may be reduced in the presence of significant residual renal function, provided this is measured regularly (ungraded).

They suggest that patients be offered short frequent dialysis (<3 hours, five to seven sessions per week) or long duration dialysis (defined as 6–8 hours, three to six sessions per week) after considering individual patient preferences and the potential benefits of these therapies. It is recommended that the potential risks be discussed prior to commencing such therapies. Increased dialysis should be considered in the presence of difficulty controlling interdialytic weight gain, blood pressure, volume overload, or metabolic parameters such as hyperkalemia, hyperphosphatemia, or metabolic acidosis (ungraded).

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recent studies. Observational evidence suggests that longer sessions and slower rates of ultrafiltration are associated with lower mortality. A single randomized trial has demonstrated that targeting a higher urea clearance (*Kt*/*V*) does not improve mortality, but this trial does not address the question of longer hours or more frequent sessions (than the standard 3.5–4 hours three times per week). A number of small studies demonstrate clear benefits of more frequent or extended hours on the surrogate endpoints of blood pressure and serum phosphate. They also suggest that such regimes may reduce left ventricular hypertrophy. Importantly, these gains were achieved while maintaining or improving quality of life. However, conflicting results have been observed on long-term mortality. Concern has been raised about loss of residual renal function with frequent dialysis and a possible increase in vascular access complications. No randomized trials are available to inform the use of RKF in dialysis prescription.

Conclusion

Dialysis adequacy must be assessed on an individual basis with patient needs being defined in line with patient goals and circumstances. We suggest that the KDOQI guidelines form part of an adequacy assessment, but emphasize that they are insufficient alone. We suggest, based on observational evidence, a minimum dialysis time of 4 hours for patients dialyzing three times per week. This is likely to be insufficient for many patients and increasing dialysis hours (or frequency) will typically be required to achieve patient needs. We recognize that important questions, such as the level of phosphate or blood pressure required to avoid death or morbidity, remain unanswered. Further research is required to define optimal surrogate endpoints (with reference to clinical events and patient-centered outcomes) as this will allow more informed goal-setting on the part of patients and clinicians.

Notes

1 This interaction was not significant after Bonferroni correction for multiple testing.
2 $N = 95$.
3 Effect estimates are adjusted for baseline characteristics (chosen as primary analysis by study authors).
4 Median change in frequent vs. standard groups ($P = 0.05$).

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General Management of the Hemodialysis Patient

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Introduction

The care of a hemodialysis (HD) patient is typically provided in a multidisciplinary setting that includes nurses, dieticians, pharmacists, social workers, and nephrologists. It traditionally focuses on the adequacy of small solute clearance (Chapter 41), vascular access (Chapter 44), anemia (Chapter 33), and mineral bone disorders (Chapter 36). This chapter is dedicated to other important issues related to the optimal care of hemodialysis patients, including potassium, acidosis, blood pressure control (hypertension [HTN] and intradialytic hypotension [IDH]), nutrition, and cardiovascular (CV) disease. It summarizes the available evidence relevant to these general aspects of the management of the HD patient.

Potassium Metabolism

The general principles of the assessment and treatment of disorders of potassium metabolism (hypokalemia and hyperkalemia) are detailed in Chapter 60. The specific problem of potassium as it relates to patients on HD is discussed in this chapter.

Prevalence and Outcomes of Hyperkalemia

Hyperkalemia is common among HD patients. In a prospective observational study from France, the proportion of patients with a serum potassium >5 mmol/l, >5.5 mmol/l, or >6 mmol/l at any time was 73.8%, 57.9%, and 34.5%, respectively. Not surprisingly, hyperkalemia is 2.0–2.4 times more prevalent on the day of the long interdialytic interval compared to short intervals due to dietary intake and impaired renal clearance despite enhanced gastrointestinal and salivary clearances in HD patients [1]. Higher dietary potassium intake is associated with increased mortality in dialysis patients even when adjusted for its association with increased energy and protein intake as well as other nutritional parameters. However, higher vegetable intake, often considered the primary source of potassium, was associated with lower mortality in a more recent, large study [2, 3]. Other contributors to hyperkalemia in HD include acidosis as well as several medications including renin-angiotensin-aldosterone system (RAAS) inhibitors, beta-blockers, heparin, and nonsteroidal anti-inflammatory drugs.

In chronic kidney disease (CKD), there is a U-shaped association between serum potassium and mortality [4]. In HD, hyperkalemia, defined as a serum potassium of 6–6.5 mmol/l compared to normal values, is associated with an increase in hospitalization and mortality regardless of the day of the week, while a serum potassium of 5.5–6 mmol/l is associated with adverse outcomes following the long dialytic interval [5]. In the analyses of the Dialysis Outcomes and Practice Patterns Study (DOPPS) data, sudden death due to arrhythmia, cardiac arrest or hyperkalemia was associated with lower dialysate potassium, including both <1.5 and 2–2.5 meq/l compared to >3 meq/l [6], suggesting that large intradialytic potassium shifts may be harmful from a CV perspective. However, a dialysate potassium of 1 meq/l in individuals with predialysis potassium >5.5 mmol/l was protective against mortality in an adjusted Cox proportional hazards model [7]. The heterogeneity of results across large observational studies challenges any determination of the

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Table 42.1 General management of the hemodialysis patient.

Treatment	Recommendation	Certainty of evidence	Strength of recommendation
Management of hyperkalaemia	We suggest adherence to a low potassium diet, ensuring adequate dialysis prescription, prescribing a dialysate potassium of 1–4 mmol/l depending on predialysis potassium levels, and correcting acidosis	Very low	Weak
Management of metabolic acidosis	We suggest using a dialysate bicarbonate of 22–24 mmol/l and using bicarbonate rather than acetate as the form of base delivery	Very low (bicarbonate dialysate concentration) and moderate (use of bicarbonate vs. acetate)	Weak (bicarbonate concentration) and weak (bicarbonate vs acetate)
Avoidance of intradialytic hypotension	We suggest that increasing dialysis session time may reduce the risk of intradialytic hypotension. In addition, cooled dialysate, prescription of midodrine, sodium profiling and the use of biofeedback may also be used.	Moderate (increasing session time) Low (cooled dialysate, sodium profiling, use of biofeedback) Prescription of midodrine (very low)	Weak
Hypertension measurement and targets	We suggest using self- home recorded BP or ambulatory BP monitoring to guide treatment rather than measures pre or post dialysis BP where possible, but it is difficult to recommend target BP in this population based on current evidence	Low	Weak
Hypertension treatment	We suggest reducing target weight and using antihypertensive agents, and that the selection of antihypertensive agents should be guided by other comorbidities and tolerance	Low	Weak
Lipid-lowering agents	We recommend not initiating lipid-lowering therapy with a statin or ezetimibe in patients receiving HD	High	Strong
Nutrition	We suggest assessing nutritional status by using a measure such as subjective global assessment and managing malnutrition by treating the underlying cause, ensuring adequate dialysis and increasing nutritional intake. We suggest generally using oral nutrition with or without supplements, but parenteral or intradialytic therapies may be considered.	Low	Weak

GRADE assessment of the certainty of the evidence [1]: High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different* is low. Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different* is moderate. Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different* is high. Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different* is very high. **Substantially different = a large enough difference that it might affect decision-making.*

degree to which hyperkalemia itself, rather than the numerous other behavioral and health issues correlated with hyperkalemia, is causative of increased mortality.

Management of Hyperkalemia

There is very little evidence guiding when and how to treat hyperkalemia to reduce the risk of death and the strength of current recommendations is weak (Table 42.1). Randomized controlled trials (RCTs) testing treatment strategies vary in terms of how they define hyperkalemia and rarely measure the degree to which treatments reduce the risk of mortality or other patient-important outcomes. Rather, this body of literature examines the degree and rapidity with which serum potassium is reduced. Whether and how urgently to institute treatment is largely guided by the degree of hyperkalemia and whether there are associated symptoms or signs (e.g. muscle weakness, paralysis, arrhythmias). It should be emphasized that although arrhythmias are considered the primary mechanism by which hyperkalemia causes death, the typical electrocardiogram (ECG) changes of hyperkalemia do not correlate strongly with serum potassium concentration nor do ECG findings associate strongly with the risk of death [8–10].

A 2005 systematic review for emergency interventions for hyperkalemia summarized the treatment for patients with hyperkalemia in general. For HD patients, the major difference is the availability and timing of hemodialysis. In symptomatic patients, maneuvers to stabilize the myocardium and shift serum potassium intracellularly should be

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Table 42.2 Summary of findings: midodrine, cooled dialysate, sodium profiling, and biofeedback approaches to intradialytic hypotension (IDH).

	Midodrine vs. placebo [43]				
Outcomes	**No. of participants (studies)**	**Absolute number (95% CI) of patients affected per 1000 treated patients for 1 year**	**Relative effect (95% CI)**	**Quality of the evidence (GRADE)**	**Conclusion**
Intradialytic hypotension	Not estimated		Not estimable		
Nadir intradialytic systolic BP	79(6)		13.3 mmHg higher (95% CI 8.6–18.0)	Very low ●○○○	It is uncertain whether midodrine improves intradialytic systolic BP in hemodialysis
Nadir intradialytic diastolic BP	79(6)		5.9 mmHg higher (95% CI 2.7–9.1)	Very low ●○○○	It is uncertain whether midodrine improves intradialytic diastolic BP in hemodialysis
Post dialysis systolic BP	101(8)		12.4 mmHg higher (95% CI 7.5–17.7)	Very low ●○○○	It is uncertain whether midodrine improves post dialysis systolic BP in hemodialysis
Post-dialysis diastolic BP	101(8)		7.3 mmHg higher (95% CI 3.7–10.9)	Very low ●○○○	It is uncertain whether midodrine improves post dialysis diastolic BP in hemodialysis
Symptoms of IDH	Not estimated: (six studies)		Not estimable: generally, report improvement in symptoms	Very low ●○○○	It is uncertain whether midodrine improves symptoms related to IDH
Adverse events and safety	Not estimated		Not estimable: no serious adverse events reported	Very low ●○○○	It is uncertain whether midodrine is safe in patients receiving hemodialysis

	Cooled dialysate vs. standard temperature dialysate [54]				
Outcomes	**No. of participants (studies)**	**Absolute number (95% CI) of patients affected per 1000 treated patients for 1 year**	**Relative effect (95% CI)**	**Quality of the evidence (GRADE)**	**Conclusion**
Intradialytic hypotension	120 (11); 552 HD sessions	Not estimated	0.32 (0.18 to 0.56)	Low ●●○○	It is unclear whether or not using a lower dialysate temperature will reduce the frequency of intradialytic hypotension
BP changes during and after dialysis	(10)				
Dialysis adequacy	(seven studies)	Not estimated	Kt/V 0.-5 (−0.09 to −0.01)	Low ●●○○	It is unclear whether cooled dialysate reduces small solute clearance compared to standard temperature dialysate
Symptoms of discomfort	2547 dialysis sessions (nine trials)	Not estimated	2.95 (0.88 to 9.82)	Low ●●○○	Cooled dialysate may increase symptoms compared to standard temperature dialysate

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Table 42.2 (Continued)

	Cooled dialysate vs. standard temperature dialysate [54]				
Outcomes	**No. of participants (studies)**	**Absolute number (95% CI) of patients affected per 1000 treated patients for 1 year**	**Relative effect (95% CI)**	**Quality of the evidence (GRADE)**	**Conclusion**
Sodium profiling vs. standard dialysis [56]					
Outcomes	No. of participants (studies)	Absolute number (95% CI) of patients affected per 1000 treated patients for 1 year	Relative effect (95% CI)	Quality of the evidence (GRADE)	Conclusion
Intradialytic Hypotension (IDH)	3600 dialysis sessions (13)	Not estimated	Pooled OR for all profiles 0.71 (0.60–0.85) Benefit varied with profile; benefit only evidence with stepwise profiling	Very low ●○○○	It is uncertain whether or not using sodium profiling compared to standard dialysis reduces the risk of IDH
Hemodialysis with biofeedback vs. standard dialysis [61]					
Outcomes	No. of participants (studies)	Absolute number (95% CI) of patients affected per 1000 treated patients for 1 year	Relative effect (95% CI)	Quality of the evidence (GRADE)	Conclusion
Intradialytic hypotension (IDH)	266 (6)	257 (from 92 fewer to 370 fewer episodes)	0.61 (0.44–0.86)	Low ●●○○	Biofeedback may reduce the frequency of IDH compared with standard hemodialysis
Predialysis systolic BP (SBP)	266 (6)	Not estimable	3 mmHg higher (2 lower to 7 higher)	Very low ●○○○	Biofeedback makes no difference to pre dialysis SBP compared with standard hemodialysis
Post-dialysis systolic BP (DBP)	266 (6)	Not estimable	7 mmHg higher (5 to 19 mmHg higher)	Very low ●○○○	Biofeedback may result in higher post dialysis DBP compared with standard hemodialysis
Quality of life outcomes	Uncertain (3)	Not estimable	No difference seen, not quantified	Very low ●○○○	It is uncertain whether biofeedback improves quality of life compared with standard hemodialysis
Mortality	104(2)	Not estimated	0.37 (0.07–2.01)	Very low ●○○○	It is uncertain whether biofeedback improves mortality compared with standard hemodialysis

considered while waiting to initiate hemodialysis. Additionally, the use of binding resins to enhance gastrointestinal elimination of potassium may be considered, although the risks and benefits are poorly delineated, particularly in dialysis patients.

New potassium binding resins are being investigated in addition to the widely available sodium polystyrene sulfonate. These include patiromer and sodium zirconium cyclosilicate (SZC). Although trials of the new agents have primarily involved nondialysis participants, a recent phase 3a trial has shown SZC to be safe, well tolerated, and effective in controlling serum potassium compared to placebo in the hemodialysis cohort in addition to usual hemodialysis. It is too early to propose how these new, expensive agents should be used in the hemodialysis cohort [11].

Dialytic Potassium Removal

Potassium removal during dialysis occurs by diffusion and convection; for diffusive therapies it is proportional to the

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gradient between serum and dialysate potassium concentrations. Once HD is initiated, serum potassium decreases approximately 1 mmol/l during the first hour of treatment and by a further 1 mmol/l over the next 2 hours and typically removes more than 100 mmol per 4-hour session but varies depending on the HD prescription [12]. Dialysate potassium concentrations typically range from 1 to 4 mmol/l based on the predialysis serum potassium values. The safety of using very low dialysate potassium concentrations, particularly potassium-free dialysate, in hemodialysis is questioned, although there is little evidence that the risk of serious hypokalemia is substantially higher with very low potassium dialysate. High bicarbonate dialysate may enhance the likelihood of restoring normokalemia by reducing acidosis and promoting an extracellular shift of potassium whereas high glucose dialysate can impair potassium removal due to insulin secretion and intracellular shifting [13].

For HD patients with recurrent hyperkalemia, adherence to dietary potassium restriction is the first step, and the dialysis prescription should be reviewed paying particular attention to adequacy, recirculation, dialysate potassium, and dialysate bicarbonate and performing a careful review and modification if possible of any contributing medications.

Management of Metabolic Acidosis

Metabolic acidosis is the most common acid-base abnormality in patients with CKD and in patients on dialysis but this abnormality may coexist with other acid-base disorders, including respiratory disorders [14]. Acid-base balance requires bicarbonate (HCO_3) reclamation in the proximal convoluted tubule and the renal excretion of nonvolatile acids (approximately 1 meq/kg of net acid production per day from dietary protein metabolism [15]) in the form of titratable acids (TA) and ammonium (NH_4). These mechanisms are dysfunctional in advanced CKD, leading to both a nonanion gap metabolic acidosis and an anion gap metabolic acidosis due the accumulation of phosphate, sulfate, urate, and hippurate. Metabolic acidosis increases as dietary protein intake increases acid generation, but is also affected by interdialytic weight gain (IDWG), dialysis schedule, dialysate bicarbonate concentration, and non-HCO_3 anion concentrations and adequacy.

Consequences of Acidosis

Metabolic acidosis in a hemodialysis patient may be associated with several consequences including:

- increased bone resorption, reduced bone mineral density, and hyperparathyroidism [16, 17]
- increased muscle protein catabolism and protein degradation [18, 19]
- hypoalbuminemia [20]
- impaired physical function [21]
- thyroid and growth hormone abnormalities [22]
- insulin resistance [23]
- hypertriglyceridemia [24]
- reduced respiratory reserve
- increased mortality [25, 26].

Base Delivery in Dialysis

The preferred form of base delivery to dialysis patients in the dialysate is in the form of bicarbonate (HCO_3) and potentially other anions, rather than acetate, as acetate is associated with hemodynamic instability [27] (Table 42.1). Observational studies suggest high bicarbonate dialysate increases predialysis serum bicarbonate, hyperparathyroidism, serum albumin, and triceps skin-fold thickness [28, 29]. The International Society of Renal Nutrition and Metabolism recommends targeting a predialysis HCO_3 of 22–24 mmol/l to avoid protein energy wasting and the Kidney Disease Outcome Quality Initiative (KDOQI) recommends maintaining a serum CO_2 > 22 meq/l in HD patients, but there are no RCTs to support alterations in dialysate or that adding oral bicarbonate improves patient-important outcomes [30, 31] (Table 42.1).

Intradialytic Hypotension

Introduction

IDH is a reduction in blood pressure during a dialysis treatment. The variety of definitions of IDH has resulted in broad estimates of frequency ranging between 10% and 55% of dialysis treatments [34, 36]. The potential importance of even IDH is due to its association with poor outcomes, particularly cardiovascular morbidity and mortality. Presumably this is due to repeated ischemic insults to vulnerable vascular beds. However, the association between IDH and clinical outcomes may primarily be due to residual confounding rather than a causal relationship.

Proposed causes of IDH include ultrafiltration (UF) rates that exceed intravascular refilling, an inappropriate target weight loss during HD treatment, intravascular osmolality reduction, autonomic dysfunction, and decreased cardiac reserve. Risk factors for IDH include dialysis vintage, female gender, lower predialysis blood pressure (BP), and hypoalbuminemia [32–34]. Studies of interventions to prevent IDH typically focus on changes in blood pressure and have insufficient power and duration to assess whether preventing IDH reduces patient-important outcomes such as cardiovascular events or mortality.

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Definition

There is no consensus definition of IDH although a number of definitions are used in the literature [35]. These include definitions based on nadir BP, drop in BP from pre-HD level, symptoms associated with a drop in BP, a drop in BP prompting intervention, and combinations of the above. Systolic BP (SBP) nadir less than 90 mmHg in at least 30% of sessions has the most evidence showing a consistent association with mortality. There appeared to be a dose–response relationship, with more frequent IDH increasing risk for death. The addition of symptoms or intervention criteria did not increase the strength of this association. In the subset of patients with predialysis BP ≥160 mmHg, nadir BP less than 100 mmHg was strongly associated with mortality [36].

Prognosis/Pathogenesis

IDH is associated with poor outcomes, particularly cardiovascular morbidity and mortality [32, 36]. Repeated intradialytic ischemic insults to susceptible vascular beds induced by IDH are felt to be the mechanism by which IDH may cause cardiovascular events [37, 38]. Intradialytic myocardial stunning has been one marker of hemodynamic stress that has been studied. Higher ultrafiltration volumes and greater decreases in intradialytic systolic blood pressure are independent risk factors for the development of intradialytic myocardial stunning (Burton 2009). After 1 year of follow-up patients with myocardial stunning at baseline had a greater decrease in left ventricular ejection fraction and increased mortality [38]. Several interventions that lead to improvement in intradialytic hemodynamics have shown decreases in surrogate outcomes such as left ventricular mass index, intradialytic myocardial stunning, and brain white matter changes [37, 39–42].

Management

Several potential interventions exist to prevent IDH, including pharmacologic and dialysis-based interventions.

Pharmacologic interventions are not a well-studied area in the prevention of IDH. The most studied pharmacologic agent in the prevention of IDH is midodrine. Midodrine is a prodrug of desglymidodrine, an alpha-1 adrenergic receptor agonist. Midodrine is one of the most commonly used pharmacologic agents to prevent IDH. A systematic review conducted in 2004 found that midodrine as compared to control resulted in significant improvements in post-HD and nadir BP [43]. The studies were limited by small sample size, short duration, and high risk of bias. There were no RCTs of midodrine for IDH prevention. The two studies that assessed midodrine with cooled dialysate showed no effect compared to cooled dialysate alone [44, 45] (Table 42.2).

Dialysis-based interventions include longer HD session time, cooled dialysate, changes in dialysate sodium, and biofeedback dialysis.

Shorter weekly HD time, increased IDWG, and consequently higher ultrafiltration rates consistently show an association with poor outcomes, including cardiovascular morbidity and mortality [46–48]. Higher UF volume is an independent risk factor for myocardial stunning [38]. More frequent dialysis is associated with improved hemodynamic tolerability and less dialysis-induced myocardial stunning [42]. Both frequent hemodialysis network trials (frequent in-center HD and frequent nocturnal HD) demonstrated a decrease in the rate of hypotensive events requiring intervention in the frequent hemodialysis groups as compared to routine HD [49, 50]. The extended follow-up of the in-center HD trial showed decreased mortality in the more frequent HD group [51]. However, the extended follow-up of the nocturnal HD trial showed increased mortality in the more frequent HD group [52]. Whether increased dialysis frequency reduces mortality and whether any benefits are due to reducing IDH is uncertain.

Cooled dialysate compared to standard temperatures has been shown to decrease IDH, LV mass index, and myocardial stunning and protect against brain white matter changes [37, 39, 40, 53]. The reduction in IDH is mediated primarily through increased peripheral vascular resistance [40, 53]. A recent systematic review and meta-analysis of randomized trials on the topic of reduced temperature dialysate demonstrated a decrease in the rate of IDH by 70% (Table 42.2). There was a trend toward increased symptoms of discomfort in the cooled dialysate group that was not statistically significant. The trials were limited by short-term follow-up, lack of data on cardiovascular events and mortality, and low to very low quality of evidence [54]. A cluster-RCT of cooled vs. standard dialysate temperature and its effect on mortality and cardiovascular events will help to answer these questions (Major Cardiovascular and Other Patient-Important Outcomes With Personalized dialYsate TEMPerature, MY TEMP, http://ClinicalTrials.gov Identifier: NCT0262836).

Dialysate sodium concentrations affect the hemodynamic tolerability of HD. Increased dialysate sodium levels are felt to protect against a drop in serum osmolality and resultant fluid shifts out of the vascular compartment. The desire to improve the tolerability of HD by increasing dialysate sodium is tempered by the concerns over a positive sodium balance. The net positive sodium balance is thought to lead to increased thirst and IDWG, requiring increased UF rates and potentially increased IDH as a consequence. Data from the DOPPS showed an association between higher dialysate sodium and higher IDWG [55].

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The same analysis of DOPPS data showed an inverse relationship between dialysate sodium and hospitalization as well as mortality. Studies on the effect of lowering dialysate sodium on IDH have had mixed results. Some have shown no effect and others an increase in the rate of IDH when dialysate sodium has been lowered (Hussein 2017). Thus far, there are no RCTs demonstrating an effect of dialysate sodium concentration on outcomes such as mortality, cardiovascular mortality, heart failure or other patient-important outcomes. A large cluster-RCT is being conducted to establish whether dialysate sodium of 137 mmol/l reduces important outcomes compared to a dialysate sodium of 140 mmol/l (Randomized Evaluation of Sodium Dialysate Levels on Vascular Events, RESOLVE, http://ClinicalTrials.gov Identifier: NCT02823821).

Sodium profiling, where dialysate sodium concentration is adjusted throughout the dialysis treatment, may decrease the risk of IDH. The dialysate sodium concentration is initially elevated, frequently to the supraphysiologic range, and is reduced based on any one of several possible profiles. A meta-analysis compared the effects of various sodium profiles on IDH [56]. A stepwise decrease in dialysate sodium was associated with a decrease in IDH. Linear profiling was not associated with a decrease in the incidence of IDH. Many of the included studies were limited by unclear allocation concealment and blinding [56].

Sodium profiles may result in a positive, negative, or neutral net sodium balance. There are concerns about net sodium gain and its associated consequences with sodium profiling. A small crossover study of IDH prone patients evaluated sodium balance positive or neutral profiles with or without simultaneous UF profiling [57]. Positive sodium balance profiles with or without UF profiling and neutral sodium balance profiles with UF profiling reduced the incidence of intradialytic discomfort, early session termination, UF failure, and inadequate dose (Kt/V) as compared to control and neutral sodium profiles without UF profiling (Table 42.2). Positive sodium balance sodium profiling was associated with increased IDWG and UF requirements. Sodium balance neutral sodium profiling combined with UF profiling was more likely to achieve target weight than positive sodium balance profiles. However, only positive sodium balance profiles significantly increased the nadir of systolic BP compared to control.

Biofeedback dialysis is an additional dialysis-based intervention that may involve adjustments in dialysate sodium and/or UF to reduce the incidence of IDH (Table 42.2). The most commonly used form of biofeedback dialysis is blood volume guided biofeedback dialysis. This method uses measures of relative blood volume to adjust UF rate and/or dialysate conductivity/sodium to maintain relative blood volume above an individualized critical value associated with the development of IDH.

Trials of biofeedback compared to dialysis without biofeedback demonstrated less intradialytic myocardial stunning and decreased rates of IDH [58–60]. A meta-analysis conducted in 2013 found biofeedback dialysis was associated with a reduced rate of IDH as compared to standard HD. The majority of included studies (6/8) used biofeedback dialysis with alterations in both UF rate and dialysate conductivity to maintain hemodynamic stability. The studies were limited by small sample size, short duration of follow-up, and low quality of evidence due to risk of bias from lack of blinding and potential for publication bias [61]. There is no high-quality evidence that biofeedback improves patient-important outcomes.

Trials of blood volume guided biofeedback dialysis where only UF rate is adjusted have not shown similar benefits. An early trial of blood volume guided HD with operator adjustments of UF rate showed an increased rate of hospitalization and mortality in the blood volume guided HD group and no decrease in the rate of IDH [62]. A recent crossover trial of biofeedback dialysis with UF rate adjustments alone in IDH prone patients did not find a significant decrease in the rate of IDH as compared to standard of care [63].

Summary

IDH is a common issue in chronic hemodialysis patients. It is associated with poor outcomes, including increased cardiovascular morbidity and mortality. While many interventions have been proposed to prevent IDH few have a solid evidence base. The literature is complicated by the fact that there have been a number of different definitions of IDH in use. There is a theoretical framework and biological plausibility potentially causally linking IDH to cardiovascular morbidity and mortality. However, critical evidence demonstrating that decreasing the incidence of IDH improves patient important outcomes such as cardiovascular events and mortality is lacking (Table 42.1).

Hypertension

Introduction

Blood pressures that meet the definition of hypertension for nondialysis patients are common in HD patients. However, whether similar definitions of hypertension are relevant to the hemodialysis patient population is uncertain and studies use heterogeneous definitions in hemodialysis. Differences arise between studies based

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on definitions that vary in terms of blood pressure thresholds, timing of measurements (predialysis, during dialysis, post-dialysis, or on nondialysis days) and methods of measurement (e.g. at dialysis, home monitoring, ambulatory monitoring). For example, in study of 355 HD patients using thresholds of 140/90 for midweek, immediately predialysis BP, and 135/85 for 44-hour ambulatory blood pressure monitoring (ABPM), 35% or 47% had HTN which was associated with a hazard ratios for mortality of 1.87 (95% confidence interval [CI]) [64]. KDOQI guidelines define HTN in HD patients as predialysis BP >140/90 mmHg or postdialysis BP >130/80 mmHg [65]. European Renal Association–European Dialysis and Transplant Association (ERA-EDTA) guidelines use home BP >135/85 mmHg, ABPM>130/80, and midweek office BP >140/90 mmHg with no recommendation for blood pressure measured at dialysis treatments [66].

Pathophysiology

HTN often reflects inadequate volume control in HD patients. The removal of excess sodium by reducing dry weight can result in normalization of BP in many cases with a lag phenomenon supported by some [67] but not all studies [68]. BP is related to many factors, including volume status, which increases postdialysis linearly but with fluctuations [69], but also sympathetic nervous system activity, the RAAS, arteriosclerosis, and drugs (e.g. erythropoietin-stimulating agents).

Measurement and Outcomes

Options for monitoring BP include predialysis and postdialysis BP measurements, self-recorded home BP (SHBP) monitoring, and ABPM (Table 42.1). ABPM and SHBP monitoring correlate with outcomes while dialysis measurements do not appear to be as reliable with predialysis overestimating and postdialysis underestimating BP reading related to changes in volume status [70]. There is a J- or U-shaped curve for BP and mortality in the HD population but most studies are based on predialysis BP measurements [71] and do not distinguish between BP lowering by therapies (e.g. probing dry weight, antihypertensives) or confounders (e.g. infection, CV disease). For example, in a Cox regression model of 24 525 HD patients from DOPPS (excluding predialysis SBP < 110 and DBP < 50 suggestive of comorbid illness) adjusted for confounders, all-cause mortality was elevated with SBP 110–129 mmHg and lower with SBP 150–159 mmHg as compared to 130–139 mmHg. Mortality was elevated with DBP 50–59 mmHg compared to 80–90 mmHg [72].

Blood Pressure Targets

The optimal BP target is uncertain in HD, with no large RCTs evaluating intensive versus liberal BP targets in contrast to CKD and the general population. A pilot trial of dialysis patients with a predialysis SBP > 155 mmHg randomized participants to a target predialysis SBP 110–140 mmHg ($n = 62$) or 155–165 mmHg ($n = 64$) for 1 year. Dry weight probing, beta-blockers, and inhibitors of the RAAS were allowed [73]. SBP between the two groups differed by 12.9 mmHg and there was an excess of hospitalizations, vascular access thrombosis, and intradialytic hypotension in the lower target group.

Blood Pressuring Lowering Therapies

Nonpharmacologic therapies to lower BP include gradually reducing the dry weight to achieve euvolemia (e.g. no symptoms of signs of hypovolemia or hypervolemia) and sodium restriction to reduce interdialytic weight gain. Additional hemodialysis treatment time or sessions may be necessary to safely achieve euvolemia. Reducing the dialysate sodium may also reduce IDWG, volume status, and BP control [74]. In the DRIP trial, a RCT comparing ultrafiltration (weight loss of 0.1 kg/10 kg per dialysis until signs or symptoms of hypotension) ($n = 100$) to physician visits only ($n = 50$) without any changes in hypertensive therapy in HD patients with a mean interdialytic ABPM of 135/75 and a postdialysis weight reduction of 0.9 kg at 4 weeks resulted in SBP −6.9 mmHg (95% CI −12.4 to −1.3, $P = 0.016$) and DBP −3.3 mmHg (95% CI −12.2 to 1.0, $P = 0.048$) with similar changes at 8 weeks, which does not support the lag phenomenon [68].

The treatment of HTN with antihypertensive agents to lower BP decreased cardiovascular events and mortality [75, 76] (Table 42.1). In a meta-analysis of eight RCTs (1679 patients including both HD and peritoneal dialysis with varying inclusion criteria) for BP lowering in dialysis patients, the weighted mean SBP was 4.5 mmHg lower and diastolic blood pressure (DBP) 2.3 mmHg lower in actively treated patients compared to controls. Any BP lowering treatment (which included carvedilol, rampiril, fosinopril, telmisartan, candesartan, losartan, and amlodipine) reduced the risk of CV events (risk ratio [RR] 0.71, 95% CI 0.55–0.92, $P = 0.009$), CV mortality (RR 0.71, 95% CI 0.50–0.99, $P = 0.044$) and all-cause mortality (RR 0.80, 95% CI 0.66–0.96, $P = 0.014$) compared to control regimens [75].

Although the above meta-analysis suggests benefits to treatment with antihypertensives, whether classes of drugs differ importantly from one another was not clear. Small trials comparing classes of drugs do suggest differences in tolerability and adverse events. For example a RCT

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compared lisonopril ($n = 100$) to atenolol ($n = 100$) in HD patients with HTN defined by ambulatory blood pressure > 135/85 and left ventricular hypertrophy (LVH). The trial was stopped early for potential excess harms in lisonopril-treated patients, including serious adverse events, hospitalization, HTN, and hyperkalemia [77]. However, excess harm was not seen in trials comparing other angiotensin blocking drugs to controls [78].

Selection of antihypertensives may be based on extrapolating evidence from the nondialysis population with specific indications (e.g. beta-blockers or RAAS inhibition for patients with reduced left ventricular function [79]). Options include beta-blockers with consideration of dialyzability [80], angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blocker (ARB) (reduction in LV mass but not CV events in a meta-analysis of five RCTs with BP 120–170/70–80), dihydropyridine calcium channel blockers, alpha-blockers, clonidine, mineralocorticoid receptor antagonists (BP lowering ranging from 1.7–11 vs. 2–5.2 in controls, RR CV mortality 0.40, 95% 0.15–0.75, RR mortality 0.40, 95% CI 0.23–0.69 [81]) and minoxidil. The use of RAAS inhibition was associated with less mortality in DOPPS with a hazard ratio of 0.89 (95% CI 0.80–0.99) and 0.94 (95% CI 0.90–0.99) in 11 241 incident and 37 124 prevalent HD patients [82]. However, in an RCT comparing olmesartan ($n = 235$) to control ($n = 234$) in HD patients with average pre-HD BP >140/90 targeting BP <140/90 did not show any difference in between the composite of death, nonfatal stroke, nonfatal myocardial infarction, and coronary vascularization. Thus, ideal targets and therapeutic agents remain uncertain.

Resistant Hypertension

Resistant hypertension in HD may be due to inadequate volume control or nonadherence in addition to other secondary causes of HTN. Paradoxical hypertension can occur during hemodialysis, possibly related the dialyzability of antihypertensives, neurohormonal activation, an altered balance of vasoactive substances, endothelial dysfunction, and hypervolemia [83]. The approach to these conditions is similar to that already outlined, including reducing dry weight, lowering sodium concentration in dialysate, and preferentially utilizing nondialyzable antihypertensives.

Statin Therapy in Patients on Hemodialysis

There have been a number of RCTs evaluating low-density lipoprotein (LDL) lowering with statin-based regimens in patients with end-stage renal disease (ESRD) to prevent vascular events. The major trials of statin use exclusively in patients with ESRD were the 4D [84] and AURORA [85] trials. Neither 4D nor ARORA demonstrated a statistical benefit of LDL lowering with statin-based regimens on their composite endpoint of cardiovascular death, nonfatal myocardial infraction (MI) or stroke. The 4D trial did show a benefit on the secondary endpoint of combined cardiac events (RR 0.82; 95% CI 0.68–0.99, $P = 0.03$).

The Study of Heart and Renal Protection (SHARP) trial examined the role of lipid lowering with a statin and ezetimibe regimen in patients with CKD. One-third of the patients with CKD enrolled in the SHARP trial were on dialysis at the outset of the trial [86]. The SHARP trial demonstrated a significant benefit of simvastatin plus ezetimibe in patients with CKD on the outcome of first major atherosclerotic event. This benefit was consistent with the previous trials of statins in patients with normal renal function when adjusted for LDL lowering achieved. Within the subgroup of patients on dialysis in the SHARP trial there was no statistically significant benefit of LDL lowering therapy. SHARP was not powered to assess the subgroup of patients on dialysis. There was no statistical evidence that the effects in patients on dialysis differed significantly from the beneficial effect seen in patients with CKD not on dialysis but, as in most trials, there was limited power to detect such difference in effect.

The Cholesterol Treatment Trialists (CTT) conducted a meta-analysis on the topic of the effect of CKD on LDL lowering with statin-based regimens using individual participant level data [87]. There was evidence that statin therapy lowered the risk of vascular events in patients with CKD not on dialysis. Even when accounting for the smaller decreases in LDL seen in CKD this relative benefit declined proportionately with estimated glomerular filtration rate (eGFR). There was little evidence of any benefit in patients on dialysis [87]. A Cochrane Review on the topic of statins in patients on dialysis found similar results showing no significant benefit of statin therapy on mortality or cardiovascular events [88].

On the basis of these studies, there is no compelling evidence that initiation of hemodialysis is an indication for statin therapy to prevent cardiovascular events (Table 42.1). By the same token, there is no compelling evidence that patients already receiving a statin at the time of hemodialysis initiation should have the statin discontinued since patients with a historical indication for statin therapy were not studied.

Nutrition

Introduction

Malnutrition is reported in up to 72% of adult patients receiving hemodialysis. Chronic inflammation and

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cardiovascular disease are commonly associated with the development of malnutrition, leading to the concept of the malnutrition–inflammation–atherosclerosis syndrome. The International Society of Renal Nutrition recommends the term protein-energy wasting syndrome, rather than malnutrition, to better characterize the loss of body protein and fuel reserves in patients receiving hemodialysis, which may be independent of nutritional intake. While some studies demonstrated declining nutritional status was associated with adverse outcomes in hemodialysis patients, this finding was not universal. Whether discrepancies between results reflect the use of different nutritional markers, measurement error inherent in assessing nutritional status, or whether poor nutrition is not truly causative of poor outcome but rather reflects declining health for other reasons, remains uncertain. However, since poor nutrition is reasonably likely to be at least partially causative of malnutrition/protein-energy wasting and its associated poor outcomes, it is commonly perceived as a therapeutic target.

Assessment of Nutritional Status

Clinical practice guidelines developed in Australasia, Canada, Europe, the UK, and the USA made specific recommendations to assess nutritional status in hemodialysis patients. Although these guidelines differed in terms of the method of assessing nutritional status, they all suggest a combination of measures should be used (Table 42.1). The most commonly recommended assessment methods follow.

Subjective Global Assessment

The Subjective Global Assessment (SGA) is the most commonly recommended method and includes an evaluation of gastrointestinal symptoms (appetite, anorexia, nausea, vomiting, diarrhea), weight change over time, functional impairment, and a visual examination of subcutaneous tissue and muscle mass. While the SGA is inexpensive and easy to perform, it has not been rigorously validated as a measure of malnutrition and may be insensitive to nonsevere forms of malnutrition.

Markers of Visceral Protein Stores

Like SGA, markers of visceral protein stores, for example serum albumin, are commonly recommended to assess malnutrition. However, serum albumin decreases with systemic inflammation and other factors not associated with nutrition. Other potentially useful markers of nutrition include serum creatinine and thyroid binding protein (prealbumin or more correctly transthyretin). Plasma creatinine concentrations reflect muscle mass, dietary protein, residual kidney function, and dialysis clearance, in addition to nutritional status. Blood transthyretin concentrations change rapidly in response to changes in hepatic protein production and may add prognostic information independent of albumin concentrations. Overall, the degree to which these are markers of malnutrition or are prognostic markers independent of nutrition is unclear.

Dietary Protein Intake

A measure of dietary protein intake is commonly recommended and may best reflect the role of nutritional intervention. Food diaries, including mobile applications or food intake recall instruments, are the most common way to measure dietary protein intake. A simple method free of recall bias is to measure protein nitrogen appearance (PNA), a proxy for protein catabolic rate and roughly equivalent to protein intake. PNA can be calculated from total nitrogen appearance (the sum of dialysis, urine, and fecal nitrogen losses) and should be normalized to fat-free, edema-free standardized body weight. Since measuring nitrogen in stool is difficult, equations estimate PNA from nitrogen in serum, urine, and dialysate. These equations are more accurate in peritoneal dialysis patients, in whom dialysate urea concentrations can be measured directly rather than estimated.

Assessment of Changes in Lean Body Mass

Lean body mass may be estimated using anthropometrics, multifrequency bioimpedance assay (BIA), and dual-energy X-ray absorptiometry (DEXA). BIA parameters indicative of poor nutritional status predicts mortality in dialysis patients. DEXA measurements are reproducible but the degree to which they associate with mortality in dialysis patients is uncertain. Hand grip strength is a simple marker of muscle mass and predicted clinical events in men but not women in one study of patients receiving hemodialysis.

Management of Malnutrition

The general principles of treating a patient receiving hemodialysis who is malnourished are (i) to treat any underlying cause (e.g. infection, heart failure, depression etc.), (ii) to ensure the patient is receiving adequate dialysis, and (iii) to increase nutritional intake. While the first of these principles does not have any evidence to guide it, it seems logical and at low risk of causing harm. The second principle is

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guided by the observations that some individuals with lower small solute clearance are more likely to have protein-energy wasting. However, in the HEMO trial that compared a higher dialysis dose (average delivered *Kt*/*V* of 1.53) to a lower dose (average delivered *Kt*/*V* 1.10) there was no evidence that a higher dose improved markers of nutritional status [89] (HEMO). Similarly, in the Frequent Hemodialysis Network trial, daily dialysis did not improve markers of nutrition [90].

Although intensive nutritional support may improve markers of poor nutritional status, it is uncertain whether this translates to improved survival, function or quality of life for patients receiving dialysis. Having said that, increasing nutritional intake may start with dietary advice/counseling and encouraging intake of food with or without supplements (Table 42.1). RCTs of nutritional supplements compared to standard diets appear to increase markers of nutrition (e.g. serum albumin and lean body mass) but it is uncertain if they improve quality of life, physical or mental function, or survival. These trials tend to be at high risk of bias (unblinded, unclear allocation methods) and have small sample sizes.

If oral nutrition is not feasible, tolerated or does not improve markers of nutrition, enteral feeding is an option for some. Similar to supplements, enteral feeding appears to improve markers of nutritional status but its effect on patient-important outcomes is unclear.

Finally, one may consider parenteral nutrition, either intradialytic or total parenteral nutrition. While these may also improve markers of nutritional status in small, randomized trials at high risk of bias, they have also not demonstrated benefits in patient important outcomes. For both enteral and parenteral feeding, understanding the risk of harm is less well delineated than estimating benefits. Risks are often extrapolated from other populations which may or may not be broadly similar to hemodialysis patients.

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43

Infections in Hemodialysis Patients

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Introduction

As the global rates of hypertension and diabetes continue to rise, the burden on end-stage kidney disease (ESKD) progression is steadily increasing [1–3] such that the prevalence of patients on hemodialysis (HD) has nearly doubled since 1990 [2]. However, the long-term survival of patients on HD can be compromised by cardiovascular events and infections [4–9].

Infections are the second leading cause of death after cardiovascular disease among HD patients and are on the rise [6, 10]. This rise in infection-related hospitalizations over the last decade has driven healthcare providers and policymakers from the Center for Disease Control (CDC) and American Society of Nephrology to embark on an initiative aimed at reducing infectious complications among in-center hemodialysis patients. This initiative, called Nephrologist Transforming Dialysis Safety, focuses on infection prevention to reduce mortality and morbidity among HD patients [11, 12].

Additionally, vascular access related infections among HD patients were historically felt to be one of the most important vascular access outcomes [13, 14]. Vascular access related infections are more prevalent in patients with central venous catheters (CVCs) than those with arteriovenous grafts (AVGs) and arteriovenous fistulas (AVFs) [13]. The 2012 United States Renal Data System (USRDS) annual data report revealed a fourfold increase in risk of infectious complications in patients initiating dialysis with a CVC compared to either a fistula or graft [15, 16]. In North America, 20–30% of patients have a catheter as their prevalent form of access [17]. The increase in prevalence of CVC use is likely due to the changing demographics of HD patients, older age and a greater burden of comorbidities, including diabetes and cardiovascular disease [18].

Higher prevalence of multidrug-resistant organisms poses additional challenges. Antibiotic overuse with an increase in patient-to-patient transmission of resistant organisms are leading factors accounting for this increase [19, 20]. Infections caused by resistant microorganisms are associated with a two to five times higher morbidity and mortality rate compared to antimicrobial susceptible microorganisms [21] and account for 23 000 deaths annually in the United States with an associated cost of more than US$20 billion [22].

Bloodborne viral infections including hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV) also poses risk among HD patients. The extracorporeal nature of HD along with occasional transfusion requirements increases the risk of bloodborne viral infections [7]. This is further amplified if there is a breakdown in infection-control practices.

In this chapter, we will describe in further detail risk factors for vascular and nonvascular infections in HD patients. We will also discuss the current evidence for prevention and management of various infections. Additionally, given the increasing resistance patterns of pathogenic microorganisms, we will highlight the risks of common nosocomial and bloodborne viral infections among HD patients.

Definition

Infections among HD patients can be classified into two main groups: vascular access and nonvascular access related infections. Vascular access infections among HD patients are usually defined as localized or systemic and simple or complicated. Localized infections are confined to

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the access site and may be associated with overlying cellulitis or purulent drainage. In patients with catheter-related bloodstream infections (CRBSIs) (see Table 43.2 for definitions), the most sensitive clinical symptom is fever or chills, which is seen in about 60–80% of patients with positive blood cultures [23–26]. Patients can also present with nausea, vomiting, altered mental status, hypotension, and other clinical features of sepsis [26]. Vascular access sites, AVFs, AVGs, and CVCs are the most common site of infection among HD patients [27, 28]. Patients on HD are also at an increased risk for nonvascular access related infections such as bacterial and viral pneumonia, *Clostridium diffiicile* associated diarrheal illness, and many other nosocomial infections.

Epidemiology

At baseline, HD patients have a mortality rate that is 100–300 times greater than that of the general population [29]. The Hemodialysis (HEMO) study showed that overall probability of death due to an infection-related hospitalization was about 15% among HD patients [30]. This increased morbidity and mortality risk from infections is multifactorial, with the main influencing risks being pathogenicity, transmissibility, frequency of infections, and host-specific factors. Host-specific factors include impairments in immune system function and the management of these patients can be challenging given the inherent susceptibility to infections [31]. From a health systems perspective, infections and related complications in HD patients account for significant costs. CRBSIs account for the majority of costs related to CVCs [32] and include indirect and direct costs associated with hospitalization, treatment and CVC management, which have been estimated to range from US$17 000 to US$32 000 annually in North America [32–35].

Pneumonia is the second most common infection among HD patients with a prevalence in HD patients of about 15 times that of the general population [6]. One in five patients with ESRD develops at least one episode of pneumonia within their first year on dialysis [36]. While the most common causative organism is *Streptococcus pneumoniae*, many other infectious bacterial organisms, seasonal influenza, or a superimposed bacterial infection after viral infection are seen in this vulnerable population.

Nosocomial infections pose additional challenges in the management of HD patients as they tend to be more resistant to usual antimicrobial treatment. Prospective results have shown that hospital length of stay is doubled in HD patients when compared to the general population with nosocomial infections [37]. The increase in morbidity stems from the alteration of naturally occurring flora with recurrent use of antibiotics [38]. Consequently, these practices confer resistance and give rise to methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococcus (VRE), and extended-spectrum beta lactamase (EBSL) organisms [39–41]. Beyond the risk of resistant organisms from antibiotic overuse, HD patients are more susceptible to an increase in *Clostridium difficile* infections [42].

Pathophysiology

CRBSIs are believed to occur via extraluminal or intraluminal routes by microbes originating from the skin or via contaminated fluids [43]. Catheters can also become innoculated by hematogenous spread of microorganisms (Figure 43.1). Observational data demonstrates that extraluminal spread is more common in catheters with a shorter duration of time (<10–14 days), whereas intraluminal spread predominates in prolonged catheterization [44, 45]. Intraluminal colonization is also likely to occur with prolonged catheterization, with one study showing 40–50% of catheters were covered with biofilms with catheters in place for >30 days [46].

Biofilms are an aggregation of bacterial organisms that form extracellular polysaccharides (EPSs) and produce adhesins, adhering to prosthetic material (CVC or AVG), accounting for persistence in infections [47]. Figure 43.2 outlines the phases of biofilm production: planktonic, adhesion, maturation, and detachment. Studies have demonstrated that antibiotic concentrations must be 100–1000 times greater than usual to kill stagnant bacteria (biofilm) versus planktonic bacteria in the bloodstream [48–51].

In HD patients, biofilms can also lead to sporadic dissemination of bacteria into the bloodstream, leading to complications [47] including metastatic deposits in the form of infective endocarditis, discitis, epidural abscess, osteomyelitis, septic arthritis, septic emboli or other complications leading to death [5, 24, 52–58]. Vascular access may also be compromised by thrombosis or deep-seated infections requiring surgical extraction to achieve source control [59, 60]. Metastatic infections complicate about 5–10% of CRBSIs with the most common being infective endocarditis, and the most common pathogens are *S. aureus* and coagulase-negative staphylococcal (CNST) organisms. *S. aureus* has an increased propensity to cause disseminated infections, with metastatic complications seen in about 30% of HD patients [61].

Diagnosis

HD patients can have a variety of presentations related to the underlying cause of infection. Clinical manifestations

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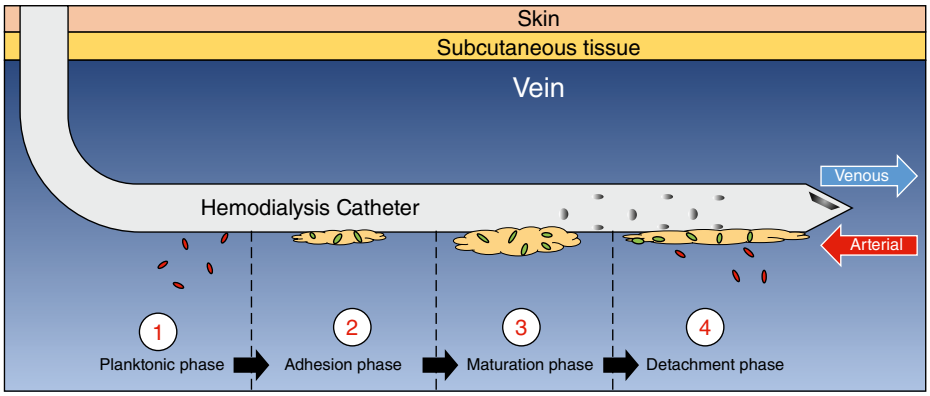

Figure 43.1 Microbial sources of catheter-related blood stream infections (CRBSIs). Microorganisms can be spread via three routes in CRBSIs: extraluminal, intraluminal, and hematogenous. Extraluminal spread is associated with colonization of the exit site by skin flora and can also be related to contamination of the exit site due to the lack of aseptic techniques. Microorganisms can be spread through the intraluminal route due to infusion of contaminated fluid or medication. Whereas, deep-seated infections entering the bloodstream give rise to CRBSIs via hematogenous spread.

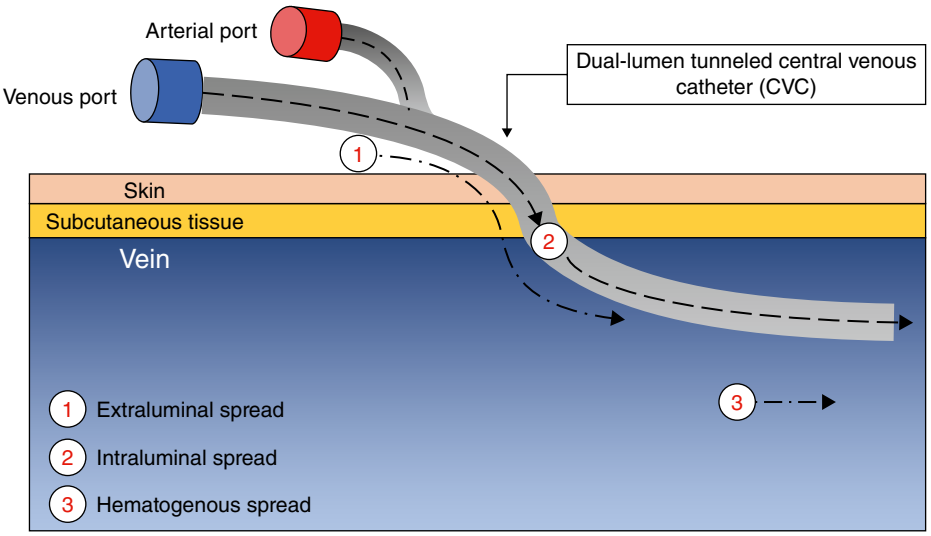

Figure 43.2 Schematic illustration of biofilm formation on central venous catheters (CVCs). (1) Planktonic phase: the bacteria are mobile in the bloodstream and may originate from intraluminal, extraluminal, or hematogenous sources. (2) Adhesion phase: bacteria attach to prosthetic material by production of adhesins to become sessile. (3) Maturation phase: bacterial organisms multiply and produce extracellular polysaccharide (EPS), leading to biofilm development. (4) Detachment phase: planktonic bacteria are released from biofilm which has matured.

may include fever, chills, nausea, vomiting, cough, hemodynamic instability, and altered mental status for both vascular and nonvascular related infections. Vascular access related infections, particularly CRBSIs, have a variety of clinical definitions with no consensus on a common definition. For example, despite the lack of consensus on a definition between the CDC, the Infectious Disease Society of America (IDSA), and the Kidney Disease Outcomes Quality Initiative (KDOQI) groups, there is some overlap in making the diagnosis of CRBSIs. Table 43.2 summarizes the differences in CBSI definitions. Regardless, patients must have positive blood cultures drawn peripherally with no other apparent source for infection along with the same organism being cultured from the catheter to make a diagnosis of CRBSI.

Although AVG infections are a less common cause for vascular access related infection, prompt recognition and diagnosis can reduce significant complications [62]. HD patients presenting with any of the following clinical features are suggestive of an infection of the AVG: overlying erythema, fluctuance, new mass or rapid development of an aneurysm, pus or prosthetic material exposure [63]. Alternatively, early graft infection can also present as thrombosis or bleeding at the cannulation site and may

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Table 43.1 Treatment and prevention of infections in hemodialysis (HD) patients.

Strategy	Recommendation	Certainty of evidence	Strength of recommendation
Catheter-based treatment and prevention strategies			
Antimicrobial locks	We suggest antibacterial lumen locks be considered in HD patients with a very low degree of certainty that there is reduction in central venous CRBSI Patients receiving this therapy with systemic antibiotics for infection have better response rates and lower recurrences of infection based on a moderate degree of certainty	*Very low* (prevention of CRBSI) *Moderate* (adjuvant treatment of CRBSI)	Weak [1–3]
Impregnated catheters	We suggest the use of impregnated central venous catheters with minocycline/rifampin or chlorhexidine/silver sulfadiazine to reduce the risk of CRBSI with a high degree of certainty	*Low*	*Weak* [4–6]
Vascular access removal	We suggest that removal of central venous catheters be done in cases with metastatic complications, persistent bacteremia or infection with *Staphylococcus aureus*, *Pseudomonas* spp. and fungal organisms with a high degree of certainty in treating CRBSI	*High*	Weak [3]
Cannulation and topical prevention strategies			
Cannulation technique	We suggest that cannulation of AVF with the rope ladder technique be utilized over buttonhole based on a high degree of certainty that it reduces vascular access related infection	*High*	Strong [7, 8]
Exit site care	We suggest topical antibiotics or povidone-iodine ointment be applied to exit sites of central venous catheters after every dressing change with a high certainty that it reduces likelihood of infection	*High*	Weak [9, 10]
Vaccination			
Pneumonia vaccines	We recommend that all HD patients barring any specific contraindications receive 23-valent polysaccharide pneumococcal vaccine every 5 years with a moderate degree of certainty that it reduces risk of contracting pneumonia	*Moderate*	Strong [11, 12]
Influenza vaccines	We recommend that all HD patients barring any specific contraindications receive annual influenza vaccines that it reduces risk of contracting pneumonia with a moderate degree of certainty	*Moderate*	Strong [11, 12]
HBV vaccine	We recommend that all HD patients barring any specific contraindications who are nonimmune to HBV receive vaccination to prevent HBV infection with a high degree of certainty	*High*	Strong [13, 14]
Bloodborne viral infections			
HCV treatment	We suggest patients with HCV infection be evaluated for treatment with an interferon-free regimen based on genotype, residual renal function, comorbities, life expectancy, and renal transplant candidacy on a moderate degree of certainty	*Moderate*	Weak [15]
HBV treatment	We suggest patients with HBV infection with active viral replication, and transaminase levels >2000 IU/ml be treated with a nucleotide or nucleoside analog on a moderate degree of certainty	*Moderate*	Weak [14]
HIV treatment	We suggest that all patients with HIV infection regardless of CD4 count be treated with antiretroviral therapy with a moderate degree of certainty	*Moderate*	Weak [16]

GRADE assessment of the certainty of the evidence: High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different* is low. Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different* is moderate. Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different* is high. Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different* is very high. **Substantially different = a large enough difference that it might affect decision-making.*
AVF, arteriovenous fistulae; CD4, ; CRBSI, catheter-related bloodstream infection; HBV, hepatitis B virus; HCV, hepatitis C virus; HD, hemodialysis.

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Table 43.2 Variations in clinical definitions of CRBSIs.

	Clinical definitions
CDC	Clinical manifestations and at least one positive peripheral blood culture and no other apparent source, with either positive semiquantitative (>15 CFU/catheter segment) or quantitative (>10 CFU/catheter segment) culture, whereby the same organism is isolated from the catheter segment and a peripheral blood sample. Simultaneous quantitative cultures of blood samples with a ratio of ≥3 : 1 (catheter vs. peripheral). A differential period of catheter culture vs. peripheral blood culture positivity of at least 2 hours. **OR** The isolation of the same organism from semiquantitative or quantitative culture segment and from blood with accompanying symptoms of bacteremia and no other apparent source of infection.
IDSA	Bacteremia or fungemia in a patient with an intravascular catheter with at least one positive blood culture and with clinical manifestations of infections and no apparent source for the bacteremia except the catheter. **AND** One of the following must be present: i) A positive semiquantitative (>15 CFU/catheter segment) or quantitative (>10^3 CFU/catheter segment) culture whereby the same organism is isolated from the catheter segment and peripheral blood. ii) Simultaneous quantitative blood culture with a >5 : 1 ratio catheter versus peripheral. iii) Differential time period of catheter culture versus peripheral blood culture.
KDOQI	**Definite:** Same organism from a semiquantitative culture of the catheter tip (>15 CFU/catheter segment) and from a blood culture in a symptomatic patient with no other apparent source of infection. **Probable:** Defervescence of symptoms after antibiotic treatment with or without removal of the catheter in the setting where blood culture confirms an infection, but the catheter tip does not or vice versa in a symptomatic patient with no other apparent source of infection. **Possible:** Defervescence of symptoms after antibiotic treatment or after removal of catheter in the absence of laboratory confirmation of bloodstream infection in a symptomatic patient with no other apparent source of infection.

CDC, Centre for Disease Control; CRBSI, catheter-related bloodstream infection; IDSA, Infectious Disease Society of America; KDQOL, Kidney Disease Outcomes Quality Initiative.
Sources: KDOQI [81], Mermel et al. [3] and O'Grady et al. [82].

mimic flow obstruction as the underlying cause of thrombosis and bleeding. Systemic symptoms with fever, chills, and other signs of sepsis along with any of the aforementioned clinical findings over the AVG should raise suspicion for infection [63]. Blood cultures should be drawn when AVG infection is suspected. It is also important to first identify the age of the AVG such as to determine whether it may be related to recent surgical graft implantation (<30 days) or due to a breakdown in sterility from recurrent cannulations required for HD [64]. Duplex ultrasonography can be used serially as an adjunct to make the diagnosis of AVG infection by evaluating graft flow and fluid collections [60, 65]. However, evaluating fluid collections with ultrasonography is limited by its lack of specificity in differentiating hematomas, seromas, and abscesses; in such cases the utilization of nuclear scans using radiolabeled techniques with technetium-99 m tagged white blood cells has been proposed [63].

Blood cultures are not always positive in patients and frequent cannulation of peripheral veins may also hinder the future creation of fistulas or grafts. A recent single-center Canadian prospective study demonstrated that blood cultures drawn from the HD circuit were most sensitive and specific in diagnosing CRBSI [66]. This practice in turn could not only reduce peripheral vein cannulation but also improve diagnostic yield of blood cultures in diagnosing CRBSIs. Therefore, if there is a high suspicion for vascular access related infection, clinicians should get two sets of blood cultures (at least one preferably from the HD circuit) and start broad-spectrum antibiotics.

Prognosis

Other prognostic factors beyond immune system dysregulation in HD patients include the type and location of access site along with cannulation methods utilized. For example, CRBSIs account for a two- to threefold increase in infection risk, hospitalization, and death compared to an AVF or AVG [67]. Observational studies have also reported an incidence of five infection episodes/1000 catheter days but there is significant variation across different types of vascular access [23, 53, 68]. Among hemodialysis catheters, tunneled cuffed lines carry a lower risk of infection compared to lines that are not tunneled [23, 68–70].

However, disagreement exists among practitioners as to whether the site of CVC is a major risk factor for developing catheter-related infections. A recent observational study from China suggested that the femoral vein site carries the highest risk for all types of catheter-related infections regardless of whether it is tunneled or not

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(Table 43.3) [71]. However, data on this point are inconsistent. In the ICU literature some studies show the femoral vein position to be worse than other sites while others don't show this consistent relationship [72, 73]. Importantly, it is unclear if these results translate to noncritically ill HD patients, but the data do suggest that a certain subset of patients with higher body mass index may be at increased risk for infection with femoral catheters. Despite the conflicting data, the CDC still recommends that catheters be placed at other sites over the femoral site to reduce risk of infection [74]. Most importantly, catheter insertion site must be prioritized according to the care plan and patient specific needs until more data becomes available.

The lowest risk of infection has been identified in patients with primary AVF [75]. A small Canadian study revealed that bacteremia rates were about 10 times greater in AVGs compared to AVFs with 2.5 and 0.2 episodes per 1000 dialysis sessions, respectively [76]. AVG infection has been identified as one of the leading causes of graft loss among HD patients, accounting for about 35% of cases [77].

Although buttonhole techniques cannot be utilized in patients with AVGs, there are still variations in cannulation methods used for AVFs which may present differing risks for developing local and systemic infections. Recent randomized controlled trials and a systematic review have revealed that patients who use buttonhole compared to rope-ladder cannulation techniques for AVF have an increased risk of infection and a slight increase in risk of metastatic complications arising from *S. aureus* bacteremia [78, 93]. Additionally, the most recent and largest randomized trial yet has shown that buttonhole cannulations were associated with increased rates of localized and systemic infections [82]. Patients who perform buttonhole cannulation tend to be home HD patients and thus perform dialysis more frequently [83, 84]. Several other factors, including more frequent cannulation and deviations from routine sterile techniques, may also account for increases in risk of infection. Wong et al. [79] reported in their systematic review that buttonhole cannulation was consistently associated with higher rates of systemic and local AVF related infections.

Other confounding factors are important. Patients who have to start dialysis urgently are more likely to have a CVC access site given the time limitations required for maturation for an AVF or AVG and are more likely to be late referrals or have ESKD as a result of catastrophic acute kidney injury. Consequently, these patients may have a greater burden of disease accounting for their increased morbidity and mortality rather than factors related to their type of access [85, 86]. Furthermore, higher blood flow rates in AVF compared to CVC may account for improved dialysis adequacy and in turn better outcomes [87].

According to the 2017 USRDS data, hospitalization rates related to sepsis among hemodialysis patients has steadily increased over the last 15 years [88]. In 2012, the 3-month mortality from sepsis was about four times greater in patients who started hemodialysis with a CVC compared to those who started with an AVF [89]. Regardless, all vascular access infections pose significant risks for developing sepsis and there is general agreement among clinicians

Table 43.3 Infection rate comparison between types of catheters and location in HD patients.

	Infection rate (infections/1000 catheter days)		
Vascular access type	**CRBSI**	**Tunnel infection**	**Exit site infection**
Tunneled central venous catheter			
Right internal jugular	6.69	2.76	4.93
Left internal jugular	6.49	2.68	5.06
External jugular	6.62	2.72	5.26
Femoral vein	10.08	3.56	10.68
Subclavian vein	6.42	2.75	5.16
Nontunneled central venous catheter			
Right internal jugular	3.57	–	8.79
Left internal jugular	3.61	–	8.54
Femoral vein	9.93	–	19.66
Subclavian vein	3.75	–	8.85

CRBSI, catheter-related bloodstream infection.
Source: Wang et al. [87].

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that the primary goals must focus on prevention. Unfortunately, large randomized controlled studies to provide robust evidence are lacking. Most guidelines are formulated based on a combination of expert opinion and observational data.

Treatment

Management of Vascular Access Infections in Hemodialysis

All HD patients with vascular access infections require early treatment and close observation to reduce risk of significant complications. Patients must have their dialysis access site evaluated regularly to determine if combined surgical and medical treatment strategies are warranted. The IDSA guidelines recommend that broad-spectrum antibiotics should include vancomycin plus gram-negative rod coverage based on local microbiological patterns for treatment of CRBSIs [3, 40]. Cefazolin can be used as an alternative to vancomycin if local methicillin-resistant staphylococcal rates are low [90, 91] (Table 43.4).

Table 43.4 Recommended dosing for broad-spectrum antibiotics while awaiting blood culture results.

Broad-spectrum antibiotics and dosing*a* for patients on hemodialysis
• Vancomycin or cefazolin plus empirical gram-negative rod coverage based on local microbiological patterns
– Vancomycin*b* plus gentamicin
○ Vancomycin: 20 mg/kg loading dose infused during the last hour of hemodialysis, followed by 500 mg during the last 30 min of each subsequent hemodialysis session
○ Gentamicin (or tobramycin:) 1 mg/kg, not to exceed 100 mg after each dialysis session
– Cefazolin*b*
○ 1 g intravenously postdialysis on dialysis days
○ If patient <50 kg, 750 mg intravenously postdialysis on dialysis days
• For Candidemia
– An echinocandin
○ Caspofungin 70 mg intravenous loading dose followed by 50 mg intravenously daily
○ Micafungin 100 mg intravenously daily
○ Anidulafungin 200 mg intravenously daily loading dose, followed by 100 mg intravenously daily
– Fluconazole 200 mg orally daily
– Amphotericin-B intravenously (usually given thrice weekly; refer to other sources for specific details)

Sources: Mermel et al. [3], Fogel et al. [100] and Barth et al. [104].
[a] Broad -pectrum dosing until the blood culture results become available.
[b] Cefazolin can be used instead of vancomycin in areas where there is a low prevalence of methicillin-resistant staphylococci.

Beyond local microbiological patterns, antibiotics should also be chosen with two things in mind: (i) the feasibility of administering around or with dialysis sessions and (ii) the side effect profile (e.g. ototoxicty, reducing residual renal function). Cephalosporins can usually be given after dialysis and do not cause ototoxicity nor lead to further reductions in residual renal function as compared to their counterparts, aminoglycosides [23, 72, 73]. It is for this reason that third- or fourth-generation cephalosporins are preferred over aminoglycosides in treating gram-negative organisms.

In all HD patients with CRBSI, early source control with catheter removal is an important consideration. Catheters should be removed in a variety of clinical situations (e.g. metastatic complications, persistent bacteremia or infection with *S. aureus*, *Pseudomonas* spp. and fungal organisms) (Table 43.1) but if alternative access cannot be established then catheter salvage procedure or changes over a guidewire should be considered [26, 90]. Catheter salvage has been defined as the continued use of a catheter throughout a CRBSI and concurrent treatment occurring with a combination of systemic antibiotics and antibiotic lock therapy [26]. However, this technique should not be utilized in cases of persistent bacteremia for more than 72 hours after initial treatment, metastatic complications, concomitant exit or tunnel site infection, or infection with pseudomonal, *S. aureus*, and fungal mircoorganisms [26, 90].

In terms of definitive treatment, management must be individualized according to specific patient needs, microorganisms isolated, and the type of vascular access. Miller and colleagues [90] highlighted that treatment of a CRBSI should focus on systemic antibiotics, antimicrobial lock solutions, and catheter management. Alternatively, for AVFs or AVGs management should focus on systemic antibiotics and managing any access site complications. The surgical management of an AVG infection may require total graft excision or subtotal or partial excision to achieve source control [77, 92]. Therefore, prompt consultation with vascular surgeons is required to definitively manage and reduce morbidity when AVG infection is suspected.

Infection Prevention Strategies

i) *Antimicrobial central catheter lock techniques*

The use of catheter lock techniques with antibiotics has become a more prevalent practice in the prevention and treatment of CRBSIs. In this practice, antimicrobial solu-

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tions of varying concentrations are placed within the catheter lumen and then allowed to dwell for a period of time when the catheter is not being used for dialysis treatment [74]. Given the significant differences in patient populations, local resistance patterns, and relatively small studies, there are currently no FDA approved formulations of antimicrobial solutions for large-scale distribution [74]. The composition of solutions has been largely done with the assistance of pharmacists at local healthcare institutions. Additionally, antimicrobial solutions have also been used as flushes rather than being locked in catheters for prevention of CRBSI.

Although many randomized controlled studies and meta-analytic data have shown reductions in the rates of CRBSI, the results may have been confounded by factors such as concomitant topical antimicrobial treatment [23, 25, 73, 93–98]. Additionally, these studies have been further limited by short duration and thus the long-term sequelae of lock therapy have not been vigorously scrutinized, particularly rates of antimicrobial resistance.

It is important to note that despite the limitation of these studies, the additional benefit of antimicrobial lock solution has been identified when used in conjunction with systemic antibiotics. A systematic review of observational data involving over 1500 hemodialysis patients showed that combination antibiotic lock therapy and systemic antibiotics resulted in better outcomes than systemic antibiotics alone in treating CRBSI [78], including a lower rate of recurrent infection. This added benefit of antibiotic lock treatment hearkens back to the earlier discussion of biofilms and the need for much higher concentrations than usual doses required to eradicate sessile bacteria [47, 51, 101, 102]. However, one major potential drawback has been that antimicrobial solutions can lead to changes in local resistance patterns. This concern has been supported by recent observational studies showing an increase in gentamicin resistance when gentamicin-heparin locks were utilized as a prevention strategy for CRBSIs [101, 102].

A recent Cochrane review of over 27 studies with nearly 3000 patients suggested that antimicrobial lock solutions may be superior to heparin lock solutions in preventing CRBSIs with a low degree of certainty based on the current evidence (Table 43.5) [103]. In clinical situations where recurrent and difficult to eradicate infections persist, combination therapy with targeted antibiotic lock solutions and systemic antibiotics may be beneficial (Table 43.1). Therefore, clinical strategies should consider targeted and short duration antibiotic lock therapy to avoid conferring resistance among organisms until more data becomes available.

ii) *Other intracatheter lock techniques*

Other intracatheter lock techniques that been have shown to reduce infections include the use of recombinant tissue plasminogen activator (rt-PA) based on the results from one randomized trial. The Prevention of Dialysis Catheter Lumen Occlusion with rt-PA versus Heparin (PreCLOT study was a multicenter randomized controlled trial [104]. PreCLOT enrolled 225 HD patients and showed that patients receiving rt-PA (1 mg in each lumen) once per week had lower rates of catheter-associated bacteremia. The heparin-only group had 1.37 episodes/1000 patient days compared to 0.40 episodes/1000 patient days in the rt-PA group [104]. Despite the promising results from this study, the use and benefits of rt-PA in preventing infections may be limited to HD patients with newly inserted catheters. Therefore, additional studies are warranted before a broad recommendation on rt-PA use for infection prevention purposes can be made for all HD patients. Additionally, no meta-analytic data involving HD patients examining the use of rt-PA in reducing CRBSIs have been found from which we can propose evidence-based recommendations.

iii) *Coating or impregnation of central catheters for dialysis*

In terms of CVCs, several strategies, including impregnated lines with chlorhexidine, silver sulfadiazine, platinum/silver (e.g. silver iontophoretic), and antibiotics (minocycline, rifampin), have been developed to reduce vascular access-related infections [35, 74, 105–112]. Although impregnated catheters may cost more than standard catheters, they may reduce the risk of CRBSI and hospital-related costs of treating CRBSI [113, 114]. A majority of the studies examining impregnated catheters were conducted using triple-lumen, uncuffed catheters that were put in place for less than 30 days [74]. Although there may be some benefit in reducing infection risk in the short term, there may be an overestimation of benefit bias given the type of catheter and duration in these studies.

Catheters coated with chlorhexidine/silver sulfadiazine have evolved over the last several years. The first generation of chlorhexidine/silver sulfadiazine impregnated catheters were coated only externally whereas the second generation of catheters have evolved to include coating both inside and outside the catheter lumen [74]. There is also an increase in the external concentration of chlorhexidine that is three times greater in the second generation of catheters compared to the first [74]. Meta-analytic studies showed a significant reduction in CRBSI rates with chlorhexidine/silver sulfadiazine coated catheters when compared to standard catheters [114, 115]. Subsequent prospective studies examining second-generation catheters showed lower rates of colonization but lacked statistical power to demonstrate meaningful differences in CBRSI rates between standard and coated catheters [116–118]. Despite the aforementioned benefits of chlorhexidine

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catheters in reducing the rates of CBRSI, there have been rare reports of anaphylactic reactions [119–122]. Therefore, clinicians should be aware of this potentially life-threatening hypersensitivity reaction in patients with chlorhexidine-impregnated catheters.

Minocycline and rifampin have demonstrated short-term benefit, primarily against *Staphylococcus epidermidis* organisms [113, 114, 123]. A multicenter randomized controlled trial showed that CVCs impregnated on both the external and internal surfaces with minocycline and rifampin were associated with lower rates of infection [109]. On the other hand, there has been a theoretical risk of conferring increased antimicrobial resistance among organisms exposed to impregnated catheters. However, the reports of minocycline/rifampin-resistant organisms have been extremely low in in vitro prospective studies [124, 125]. Furthermore, there have been no previous reports in the clinical setting of resistant organisms arising from antibiotic impregnated catheters.

Although many of these studies highlighting impregnated catheters are underpowered, observational data suggests that these interventions may reduce risk of CRBSIs among hemodialysis patients (Table 43.1). Until larger trials are published that go against current practices, the benefits of impregnated catheters outweigh potential risks.

iv) *Noncatheter-based general strategies*

Other noncatheter-based infection prevention strategies should also focus on cannulation methods. Cannulation methods, particularly buttonhole cannulations, is another factor to consider that increases risk of vascular access related infection in hemodiaysis patients. At least two systematic reviews have shown good evidence that rope ladder cannulation should be utilized over buttonhole cannulation to reduce infection risk [79, 80]. Based on those reviews, we recommend that rope ladder cannulation be chosen over buttonhole technique to reduce the risk of vascular access related infections (Table 43.5).

Table 43.5 Summary of findings: catheter and cannulation-based infection prevention strategies.

Outcomes	No. of participants (no. of studies)	Events per 1000 catheter/AVF[a] days (95% CI)	Relative risk (95% CI)	Certainty of the evidence (GRADE)	Conclusion
Antimicrobial lock solutions versus heparin lock solutions					
CRBSI	2994 (27)	161 fewer (190–122 fewer)	0.38 (0.27–0.53)	Low ●●○○	Antibiotic locks may be superior to heparin compared to lock solution with low degree of certainty
Thrombosis	2080 (14)	69 fewer (158–73 fewer)	0.15 (0.03–0.81)	Very low ●○○○	It is uncertain whether there are any differences in antibiotic and heparin lock solutions in preventing catheter-related thrombosis
Antibiotic impregnated catheters versus standard catheters					
All-cause mortality	2643 (10)	50 fewer (105 fewer to 21 more)	0.92 (0.80–1.07)	High ●●●●	Antibiotic impregnated catheters do not reduce all-cause mortality compared to nonimpregnated catheters with a high degree of certainty
CRBSI	10 405 (42)	112 fewer (140–77 fewer)	0.62 (0.52–0.74)	High ●●●●	Antibiotic impregnated catheters reduce CRBSI with a high degree of certainty, particularly in the ICU setting
Buttonhole versus rope-ladder cannulation					
Infection	90 (15)	Not estimable	3.18 (2.12–4.77)	High ●●●●	Buttonhole cannulation is associated with higher rates infection (local and systemic) compared to rope ladder cannulation

CI, confidence interval; CRBSI, catheter-related bloodstream infection.
Estimates are drawn from two Cochrane reviews and one systematic review [6, 91, 114]. GRADE assessment of the certainty of the evidence: High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different* is low. Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different* is moderate. Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different* is high. Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different* is very high.
**Substantially different = a large enough difference that it might affect decision-making.*
[a] Representing patients who had an events/per 1000 AVF days with buttonhole and rope ladder cannulation.
Source: Based on Arechabala et al. [103].

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v) *Topical ointments*

The colonization of the exit site by organisms from skin flora poses a significant risk for patients to develop exit site infections and bacteremia. The application of topical antiseptic agents including chlorhexidine, povidone-iodine and antimicrobial ointments has been shown to reduce the risks of infection [74, 107, 126, 127]. In 2010, a Cochrane Review of preventative strategies against infections related to hemodialysis catheters found that there were significant reductions in CRBSIs and exit site infections with mupirocin and polysporin based-antibiotic ointments along with povidone-iodine ointment (Table 43.6) [94]. Recent observational and meta-analytic data have also suggested that chlorhexidine is superior to povidone-iodine ointments in preventing infections [35, 94, 106]. Although there are some potential drawbacks with topical solutions, including damage to silicone-based catheters, bacterial resistance, and fungal colonization, the preventative

Table 43.6 Summary of findings: topical antibiotic ointments for preventing vascular access related infections.

Outcomes	No. of participants (no. of studies)	Events per 100 000 catheter days (95% CI)	Relative risk (95% CI)	Certainty of the evidence (GRADE)	Conclusion
Topical antibiotic ointment versus no ointment					
CVC infection	193 (2)	Not estimable	0.33 (0.18–0.61)	Moderate ●●●○	Topical antibiotic ointments likely reduce CVC infections
Exit site infection	346 (4)	Not estimable	0.20 (0.09–0.45)	Moderate ●●●○	Topical antibiotic ointments likely reduce exit site infections
CRBSI	212 (2)	1051 fewer (1142–880 fewer)	0.19 (0.12–0.32)	Moderate ●●●○	Topical antibiotic ointments, particularly with mupirocin compared to no agents reduce CRBSIs
Mortality (all-cause)	332 (3)	Not estimable	0.36 (0.12–1.07)	Low ●●○○	It is uncertain whether topical antibiotics improve all-cause mortality
Mortality (infection-related)	332 (3)	Not estimable	0.15 (0.03–0.81)	Low ●●○○	It is uncertain whether topical antibiotics improve mortality related to infections
Topical honey versus antibiotic ointment					
CVC infection	– (—)	Not estimable	No studies	Absent	No studies to evaluate impact of topical honey compared to topical antibiotics on CVC infection alone
Exit site infection	150 (2)	Not estimable	0.45 (0.10–2.11)	Very low ●○○○	It is uncertain if topical honey reduces exit site infection compared to topical antibiotic ointment
CRBSI	150 (2)	337 fewer (1052 fewer–973 more)	0.83 (0.47– 1.49)	Very low ●○○○	It is uncertain if topical honey reduces CRBSIs compared to topical antibiotic ointment
Mortality (all-cause)	– (—)	Not estimable	No studies	Absent	No studies to evaluate impact of topical honey compared to topical antibiotics on all-cause mortality
Mortality (infection-related)	– (—)	Not estimable	No studies	Absent	No studies to evaluate impact of topical honey compared to topical antibiotics on infection-related mortality

CI, confidence interval; CRBSI, catheter-related bloodstream infection; CVC, central venous catheter.
Estimates are drawn from one Cochrane review [9]. GRADE assessment of the certainty of the evidence: High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different* is low. Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different* is moderate. Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different* is high. Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different* is very high. **Substantially different = a large enough difference that it might affect decision-making*.
Source: Based on McCann and Moore [94].

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benefits outweigh risks such that the CDC recommends antibiotic or povidone-iodine ointment to exit sites after every dressing change [74] (Table 43.1). Alternatively, topical agents such as honey to exit sites have shown promising results in reducing catheter-associated infections in a small randomized control study [130]. However, the small sample size in this study limits the wider adoption of honey as a topical agent on exit sites among hemodialysis patients.

As mentioned earlier, the colonization of exit sites by skin flora poses significant risk for infection among hemodialysis patients [55, 129]. Colonization of other areas beyond the exit site can also pose risks for infection. *S. aureus* is the most common nosocomial pathogen worldwide [130], associated with high morbidity and mortality rate, attributable to its widespread colonization. The nasal passage of about 25% of chronic HD patients is colonized by *S. aureus* [131]. Furthermore, given the morbidity and mortality associated with *S. aureus* infections and that a majority of infections originate from the nasal cavity, its eradication reduces risks to patients. A success rate for *S. aureus* eradication of >90% occurs with mupirocin 2% when used for 30–90 days [131, 132]. However, the success rate of eradication dramatically decreases when used beyond 90 days, possibly due to emergence of *S. aureus* resistance. Therefore, given the prevalence of *S. aureus* colonoziation among HD patients, eradication with mupirocin and wearing surgical masks at times when vascular sites are being accessed reduces risk of contamination [133, 133–135]. Additionally, the use of aseptic techniques and barriers helps further reduce infection risk with needle insertion and CVC manipulation for the initiation of dialysis [24, 26, 115]. The importance of proper aseptic practices cannot be understated as rates of infection increase when nursing staff are inadequately trained [136, 137].

Nosocomial Infections

As mentioned earlier, HD patients are at increased risk for all types of infection, including *C. difficile* associated diarrheal illness and pneumonia. The treatment of *C. difficile* in HD patients is similar to that used in the general population with some minor adjustments in the dosing for metronidazole [138, 139]. Similarly, the treatment of pneumonia is quite similar to that for the general population with alterations in dosing for renally cleared medications being the only significant difference. Furthermore, current guidelines recommend that all patients on hemodialysis should receive the annual influenza vaccine and 23-valent pneumococcal polysaccharide vaccine every 5 years provided that there are no contraindications [140–142] (Table 43.1).

Bloodborne Viral Infections

Apart from bacterial infections, HD patients are at increased risk for bloodborne viral infections, including HBV, HCV, and HIV [7]. The new 2017 Kidney Disease International Global Outcomes (KDIGO) clinical practice guidelines recommend that all HD in-center patients should be screened initially for HCV and then once every 6–12 months afterwards [143]. Additionally, all HD patients should be evaluated for treatment with an interferon-free based regimen and the choice of direct acting antiviral agent should be based on HCV genotype, viral load, drug interactions, degree of hepatic fibrosis, eGFR, and other medical comorbidities [143] (Table 43.1). In order to limit the intra-unit spread of these bloodborne viruses, hemodialysis units must ensure that there is implementation of and adherence to infection control practices. These practices will prevent the transfer of infections through contaminated fluids, equipment, and/or surfaces. Strict infection control procedures [143] are the mainstay of preventing the spread of viral infections. For patients infected with HCV and HIV, patient isolation and the use of dedicated machines is not required.

However, the practices for HBV are different and patients with positive hepatitis B surface antigen (HBsAg) should be isolated in separate rooms with dedicated machines and equipment (Table 43.7) [144, 145]. Despite the increased risk of transmission among HD patients, the prevalence of HBV infection has remained stable over the last decade owing to infection control measures, screening for infection, and vaccination [146]. The prevalence of HBsAg positivity among HD patients is also

Table 43.7 Recommended HBV precaution and isolation practices.

- Patients should be placed in a private room or segregated area
- Healthcare workers caring for patients with HBV cannot care for HBV-susceptible patients concomitantly
- Healthcare workers caring for patients with HBV should be HBV immune
- Contact precautions should be undertaken by wearing gloves and gowns
- Facial mask with eye protection with every cannulation and decannulation
- Dialyzers should not be reprocessed/reused

HBV, hepatitis B virus.
Sources: Center for Disease Control [13] and Rebmann et al. [151].

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dependent on the endemic state within the general population. In 2002, the prevalence of HBsAg positivity among HD patient was about 1% in the United States [146], whereas the prevalence of HBV infection among HD patients from most Pacific Asian countries ranges from 5% to 15% [147].

HBV maintains environmental stability by persisting on surfaces and equipment at ambient room temperatures, where it can remain infectious for up to 7 days after contamination [152]. Additionally, patients with HBV infection also tend to have high viral titers; coupled with environmental stability, this makes the risk of HBV transmission much higher than that seen with other bloodborne viruses. Additionally, HD patients with active HBV infection that are treated with a nucleotide or nucleoside analog, which reduces the overall risk of infection to other patients within a dialysis unit [148]. Treatment for acute and chronic infections are dependent on patient viral load (HBV DNA >2000 international units [IU]/ml), abnormal liver enzymes and evidence of active replication with a positive hepatitis B e antigen (HBeAg) [148].

All HD patients who are nonimmune to HBV should receive HBV vaccine in an attempt to reach the desired antibody titer of ≥10 mIU/ml. Patients receive three doses of 40 μg at three intervals (months 0, 1, and 6) and if the patient does not achieve the desired antibody titer then a repeat course of vaccination is recommended [144, 145]. If a patient still does not respond after the second course of vaccination, no further doses of intramuscularly administered vaccine are recommended [144]. However, patients who are nonresponders can be given intradermal HBV vaccine [149]. Observational studies have shown significant improvement in the rates of vaccine-induced seroconversion after intradermal administration in HD patients who did not respond initially to intramuscularly administer vaccines [150–153]. Patients who remain nonimmune to HBV despite the abovementioned strategies must be followed with monthly HBsAg as they remain susceptible for future infection.

Conclusion

Patients on hemodialysis continue to be at an extremely high risk of contracting infections. Given the degree of immune dysregulation along with increases in CVC use seen in HD patients, infection risk is further potentiated, particularly for CRBSIs. There is data showing that various prevention strategies can reduce vascular access related infections among patients. However, an approach that extends beyond aseptic technique practices, impregnated catheters, and antibiotic locks is demanded. Given the significantly higher risk of infection with CVCs compared to an AVF, tireless strategies prioritizing fistula creation are warranted. Development of infectious surveillance programs has seen tremendous success across various centers in tracking local infection rates and reducing recurrences of CRBSI, therefore all dialysis programs must consider the creation of an infection surveillance team consisting of dedicated clinical staff and resources, ensuring that timely treatment occurs. This team should also perform ongoing catheter audits and rationale for catheters in an attempt to promote a "fistula first" and "lines last" strategy to further improve clinical outcomes. Adjunctive approaches with impregnated catheters and antibiotic locks as a prevention strategy can be considered on an individual basis. However, antibiotic locks should strongly be considered in conjunction with systemic antibiotics for the treatment of CRBSIs in an attempt to eradicate biofilms on the catheter. Although some of these preventative and treatment strategies appear promising, there continues to be a lack of high-quality data to support their efficacy in HD patients. Future priorities must focus on generating data from larger and more robust studies to improve current evidence-based guidelines and in turn clinical outcomes for all HD patients.

Furthermore, HD patients are at risk for all types of infection therefore appropriate vaccinations for respiratory infections are recommended and the risk of bloodborne viral infections particularly HBV demands consistent vigilence and strict infection control procedures.

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44

Vascular Access for Hemodialysis

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Introduction

Hemodialysis is the dominant form of therapy for patients with end-stage kidney disease (ESKD) and requires repetitive, complication-free access to the peripheral blood circulation. Hence the establishment and maintenance of vascular access is pivotal and has long been labeled the Achilles heel of hemodialysis due to its vital role in the delivery of hemodialysis [28]. The provision of vascular access for hemodialysis patients therefore represents a major management focus for all nephrologists.

Definition

Vascular access for hemodialysis can be achieved in three ways: by a native arteriovenous fistula (AVF), an arteriovenous graft (AVG) (usually polytetrafluoroethylene or PTFE), or a cuffed (or uncuffed) central venous catheter (CVC) (Figure 44.1). The native AVF, first described by Brescia, Cimino, and colleagues in 1966 [29], is a surgically constructed connection between a peripheral artery and vein. The most common configurations are either at the wrist (radiocephalic AVF) or at the elbow (brachiocephalic AVF), although several other surgical configurations are used. All AVFs require time to mature before they can be used for dialysis, with time durations that can range from as low as 1 month up to 6 months.

The AVG is constructed by implanting a synthetic tube (most commonly PTFE) between an artery and a vein in the arm, usually as a loop between the cephalic artery and vein at the elbow. The major advantage of AVGs is the shorter maturation period – usually 1–2 weeks – but this is at the expense of the need for more interventions to maintain patency. Successful use of the PTFE AVG was first reported in 1976 and by the late 1980s it was the predominant vascular access used in the United States [30]. Following the preference of AVFs over AVGs by clinical guideline groups [31–34], use in the United States and other countries has declined [35].

Cuffed CVCs are tunneled subcutaneously, ideally into the right internal jugular vein but can be placed in other central veins depending on clinical circumstances. The main role of the cuffed CVC is as a bridge until either an AVF or an AVG can be constructed or kidney transplantation occurs or as permanent access in the patient who has exhausted all other vascular access possibilities.

Epidemiology

Clinical practice guidelines recommend the native AVF as the vascular access of first choice for patients treated with hemodialysis [31–34]. These recommendations derive from an assessment of vascular patency rates, infection risk, lower mortality, and lower costs. Here we discuss these recommendations and provide interpretation in relation to more recent data published since the guidelines were written.

Prior to the mid 2000s, it was clear that, compared to AVGs, AVFs had superior long-term patency rates as well as lower intervention rates to maintain patency [33]. However, with the changing demographic of the dialysis population, principally due to increasing age and comorbidity (especially diabetes mellitus and cardiovascular disease), the superiority of AVFs over AVGs in terms of patency has become less clear, specifically when AVF primary failure is considered [36]. Rates of primary failure of AVFs increased from 15–20% in 1980s and 1990s [37] to 40–50% in study cohorts assessed after 2005 [38]. Rates as high as 60% have been seen in trials addressing antiplatelet

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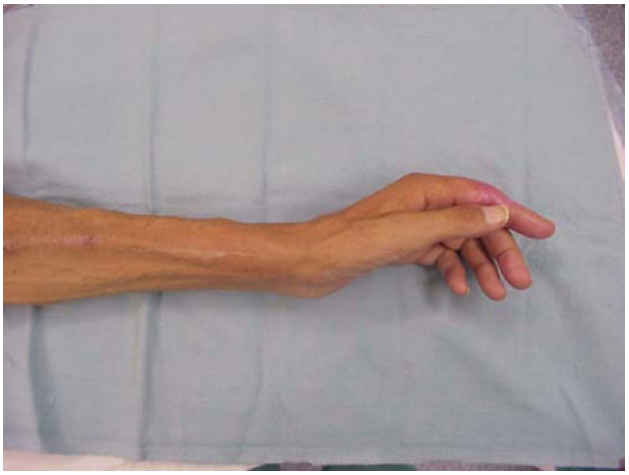

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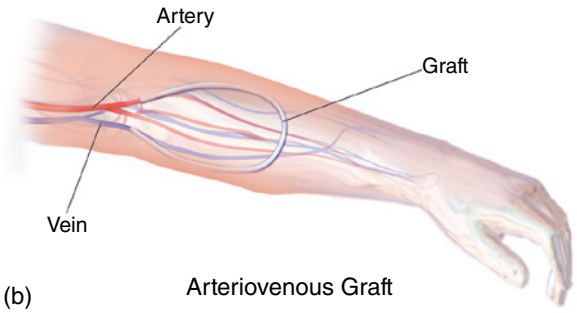

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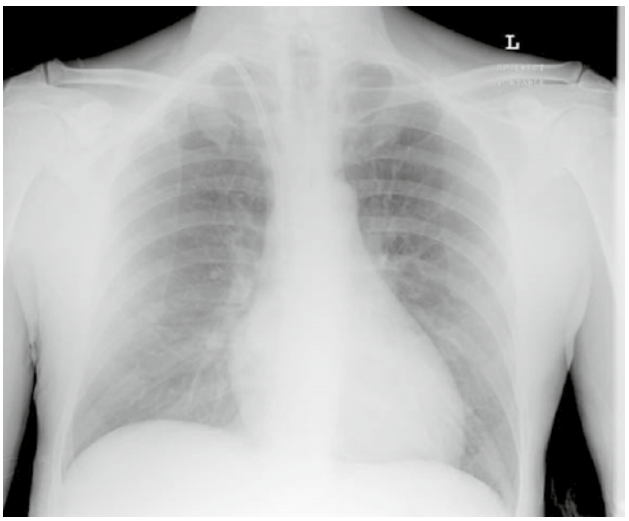

(c)

Figure 44.1 Vascular access types for hemodialysis. (a) Arteriovenous Fistula (AVF) (b) Arteriovenous Graft (AVG) (c) Central venous catheter (CVC) Source (b) : Blausen.com staff (2014). "Medical gallery of Blausen Medical 2014". WikiJournal of Medicine, 1(2). DOI:10.15347/ wjm/2014.010. ISSN 2002. Licensed under CC BY 4.0.

agents and their effect on primary AVF failure [39, 40]. However, it is clear that once an AVF has been established, the long-term intervention-free patency remains superior compared to that of an AVG [36]. Data from the Dialysis Outcomes and Practice Patterns study (DOPPS), assessing noninfectious vascular access-related complications, show that after commencement all access types experience high compilation rates in the first 6 months of dialysis, with steep declines thereafter [41]. The overall risk of complications is lowest for AVFs, highest for CVCs, and AVGs have an intermediate risk [41]. Subsequent work suggests that CVCs have a 40% lower risk of noninfectious patency complications compared to AVFs in the first 90 days after dialysis commencement, which then reverses to a 22% increase risk in the subsequent 90 days [42].

Infectious complications of vascular access are also lowest for AVFs, highest for CVCs, and intermediate for AVGs [41–43]. Infection rates for CVCs are about twice the rate for AVFs in the first 6 and 12 months following dialysis commencement [41, 42]. Catheter-related bacteremia is responsible for 70% of vascular access-related bacteremia in the United States [44] and can result in prolonged hospitalization with major compilations such as endocarditis and metastatic infections. While AVFs have the lowest rate of infection, bacteremia as a result of an infected AVF is an important complication. In particular, rates of infection are consistently higher with the use of buttonhole needling such that it should only be used in situations where rope ladder cannulation is not possible or easy [45, 46].

Mortality according to access type has been assessed in a number of different populations [47–50], with all the observational studies summarized in a recent systematic review [43]. CVC use is consistently associated with higher risk of all-cause and infectious death compared to AVF use. However, while results are consistent across multiple studies and different populations, patients who commence with a CVC are different to those using an AVF, and therefore results remain susceptible to residual confounding and indication bias. Recent data suggest that mortality rate by access type may not be directly attributable to the actual access in use [42, 51]. However, only adequately powered randomized trials can address such a question, with attempts underway to ascertain initial feasibility of such a study [52, 53].

The maintenance of vascular access in hemodialysis patients is estimated to account for at least 25% of all dialysis patient hospital admissions in the United States [54, 55]. Two early studies specifically performed a cost analysis by vascular access type [56, 57], both from Canada. The first study [57] considered the costs of maintaining a functioning access in prevalent patients, demonstrating significantly lower access-related costs per patient per year for patients who were using an AVF compared to those with an AVG and catheter. Total costs, including access-related interventions and hospital stays, were lowest for AVFs, highest for AVGs and intermediate for CVCs. The same

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group then prospectively studied the costs for the establishment and maintenance of vascular access in an incident cohort of subjects [56]. In that time, 18.4% of all hospital admissions were vascular access related. Again, the mean cost of access care per patient-year at risk was lowest for AVFs compared to catheters and AVGs: CAN$9180 for maintaining a catheter exclusively, CAN$11685 for attempting an AVG, and CAN$7989 for attempting an AVF. More recent estimates suggest that AVF costs are lowest over 2 years in those in whom primary patency of the AVF is maintained but highest in subjects who commence dialysis with a CVC and a maturing AVF in situ [58]. Patients who dialyze solely with a CVC and did not have an AVF created had higher healthcare delivery costs compared to those with a patent AVF, but significantly lower than those with a CVC and maturing AVF. Similar to the mortality question, an unbiased cost-effective analysis would require an adequately powered and designed randomized trial.

Both incidence and prevalence rates for the three vascular access types vary considerably across different countries and indeed across different jurisdictions and hospitals [59]. In the majority of countries, new ESKD patients commencing hemodialysis for the first time do so via a CVC [59]. However incident CVC rates vary from as low as 10% in Japan to 50% in the UK, Australia, and New Zealand, and 70% in the United States and Canada. Likewise, AVF/AVG prevalence rates vary significantly across countries. Canada, for example, has one of the lowest AVF/AVG prevalence rates in the developed world at approximately 55%. In contrast, the United States, which implemented the "fistula first" program, have increased the AVF prevalence rate from 30% in the early 2000s to 65% in 2016 [60]. The Australia and New Zealand AVF/AVG prevalence rates sit at 75–80% and have remained stable over the last 15 years [61], with rates in Japan consistently at 97% [60]. In addition to the prevalence rates, there is marked variation across countries in relation to anatomical location and successful usage of AVF. In Japan, more than 90% of AVFs are placed in the lower arm whereas in the United States upper arm AVFs are the most prevalent [62]. In Europe, Australia, and New Zealand lower arm AVFs make up approximately 65% of all AVFs used [62]. While differences in permanent access rates can be attributed in part to differences in patient case mix, differences in physician and healthcare practice patterns will also play an important role.

Pathophysiology

A large number of interventions aimed to prevention of vascular access dysfunction have been tested and are summarized in table 44.1. Before presenting the evidence for each treatment in detail we first discuss the pathophysiology of vascular access dysfunction.

Pathophysiology of Arteriovenous Access Dysfunction

Delivery of effective hemodialysis via an AVF or AVG requires sufficient access blood flow and an accessible conduit that can resist repeated cannulation. Failure to attain these properties is usually the result of a vascular stenosis due to neointimal hyperplasia, access thrombosis, inadequate vasodilatation and vascular remodeling or any combination of these [63]. An AVF usually takes between 1 and 9 months to be usable for dialysis and around 20% and 60% of AVFs fail to mature adequately [39, 40, 64]. AVGs can be used within days [65], but require more interventions to maintain long-term patency compared to AVFs [36].

The complex pathophysiology of neointimal hyperplasia and maladaptive vascular remodeling causing access dysfunction or failure can be conceptualized as a cascade of "upstream" and "downstream" events [66]. "Upstream" events describe factors that cause endothelial and smooth muscle cell injury, including hemodynamic shear stress due to the altered hemodynamics following creation of an arteriovenous anastomosis, surgical manipulation, repeated cannulation, angioplasties, and the use of bioincompatible graft material. These events lead to a complex "downstream" response characterized by the interplay of pro-inflammatory cytokines, chemokines, metalloproteinases, and adhesion molecules that promote cell activation, proliferation, and migration with neointimal hyperplasia formation (a fibromuscular thickening of the vascular wall composed of extracellular matrix, myofibroblasts, and differentiated contractile smooth muscle cells) and unfavorable vascular remodeling (Figure 44.2). Other modulators include the uremic milieu characterized by inflammation, oxidative stress, and endothelial dysfunction [67–69], and genetic predispositions to neointimal hyperplasia formation, vasoconstriction, inflammation, and thrombosis [63, 70–73].

Pathophysiology of CVC Dysfunction

CVCs are the least preferred hemodialysis access due to the high risk of malfunction and infection that compromises the efficacy of hemodialysis and may increase patient morbidity, mortality, and healthcare costs [41, 48, 56]. In an attempt to standardize the definition of CVC dysfunction, the Kidney Health Initiative Vascular Access Working Group of the American Society of Nephrology has proposed the following criteria: "the inability of a CVC to (i) complete a single dialysis session without triggering recurrent pressure alarms or (ii) reproducibly deliver a

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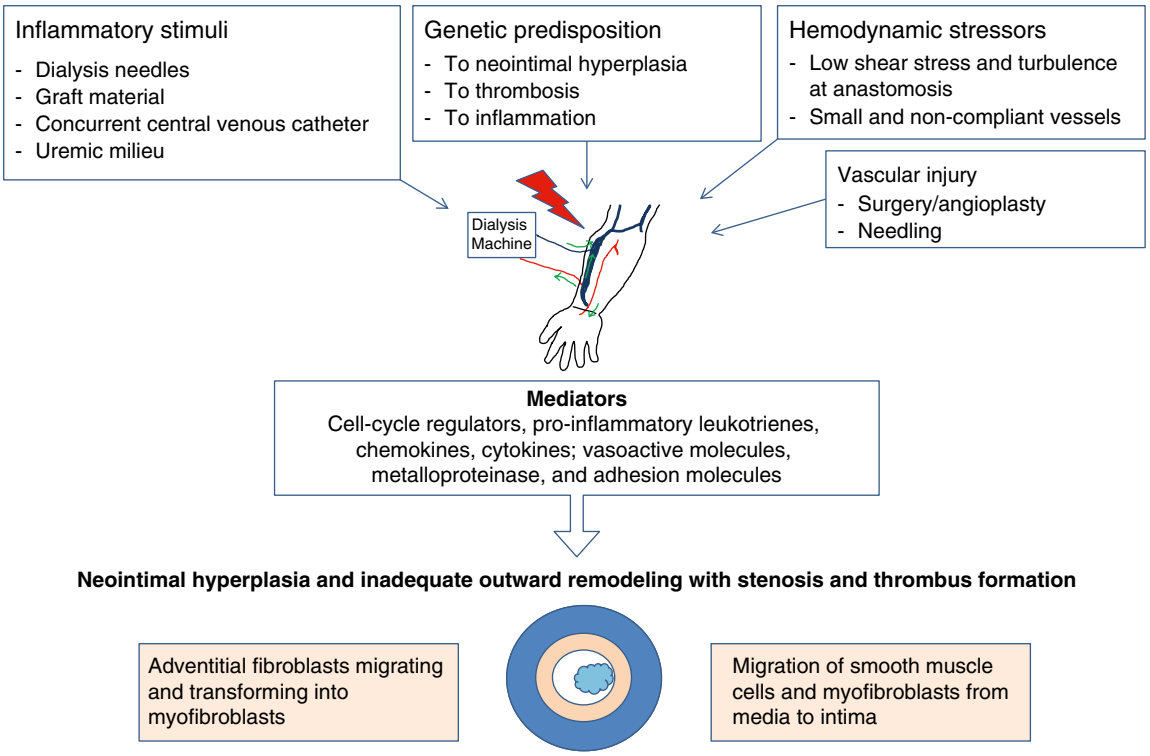

Figure 44.2 Pathogenesis of arteriovenous access failure. This figure summarizes the pathogenetic cascade of events that result in arteriovenous access failure: Hemodynamic and surgical stressors, inflammatory stimuli such as bioincompatible graft material, uremia and recurrent needling as well as genetic predisposition lead to activation of pro-inflammatory mediators that promote inadequate outward remodeling, migration and transformation of smooth muscle cells and fibroblasts with resulting neointimal hyperplasia, luminal narrowing and thrombus formation. *Source:* Viecelli et al. [98]. © 2018 John Wiley & Sons.

mean dialysis blood flow ≥300 ml/min (with arterial and venous pressures being within the hemodialysis unit parameters) or provide a Kt/V of 1.2 in 4 hours or less [74]."

Primary (early) dysfunction is typically caused by a mechanical problem including catheter malpositioning, tip malorientation, catheter kinking or constrictive sutures, and manifests during the first few catheter uses. Secondary (late) dysfunction may be the result of an intrinsic thrombosis within the catheter lumen, extrinsic thrombosis encasing the catheter and/or formation of a fibrin sheath [74] (Box 44.1). Exposure of the artificial catheter material to blood leads to protein adsorption and activation of the complement and coagulation pathways [75]. Fibrin deposition typically occurs at the site of intimal injury and can wrap the entire catheter within a few days [76]. In addition to fibrin, these sheaths contain laminin, fibronectin, collagen, and smooth muscle cells and overlying endothelial cells. Fibrin sheath formation is closely linked to biofilm formation. Biofilms are characterized by a sessile community of microorganisms that produce and embed themselves in an exopolysaccharide matrix [77, 78]. Biofilms facilitate sustained infection and subsequent hematogenous seeding of infective microorganisms, exemplifying the close interplay between catheter malfunction and catheter-related infections.

Box 44.1 Causes of Catheter Dysfunction
Primary catheter dysfunction
Incorrect catheter positioning
Incorrect vessel (azygos vein)
Tip malorientation
Tip malpositioning
Catheter kinking
Constrictive suture
Secondary catheter dysfunction
Thrombosis (intrinsic or extrinsic)
Fibrin sheath +/− biofilm

Diagnostic Tests

Formation of Permanent Vascular Access

Prior to AVF formation a thorough assessment of suitability for AVF formation should be performed. This includes taking a clinical history with emphasis on risk factors that can

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Table 44.1 Prevention of vascular access dysfunction.

Treatment	Recommendation	Certainty of evidence	Strength of recommendation
Arteriovenous access			
Pre-operative ultrasound imaging	We suggest pre-operative ultrasound imaging be considered to increase the likelihood that an AVF will be created, mature and be used for dialysis.	*Low*	Very weak [1]
Preemptive correction of stenosis	We suggest that AVF surveillance coupled with pre-emptive correction can be used to reduce AVF thrombosis and potentially reduce AVF loss. AVG surveillance coupled with pre-emptive correction should not be used to prevent AVG thrombosis or loss.	*Low* (AVF) *Moderate* (AVG)	Weak [2]
Antiplatelet agents	We suggest antiplatelet agents can be used in AVF to reduce early thrombosis and failure (thrombosis or loss of patency). Patients with an AVF or AVG may reasonably choose not to receive antiplatelet therapies based on the low certainty that treatment makes any difference to attain arteriovenous access suitability for hemodialysis or reduce access interventions and may cause bleeding.	*Moderate*[a] (early thrombosis and access failure) *Low*[a] (failure to attain suitability for dialysis, need for arteriovenous access interventions, major or minor bleeding)	Weak [3, 4]
Fish oil	We suggest fish oil supplementation can be used in AVF and AVG to reduce primary patency loss. Patients with newly created arteriovenous access may reasonably choose not to receive fish oil based on the low to very low certainty that it makes a difference to the need for interventions to maintain patency or assist maturation, dialysis suitability (AVF), arteriovenous access abandonment, hospitalizations, all-cause or cardiovascular mortality, and uncertain adverse effects including bleeding and gastrointestinal adverse effects related to treatment.	*Moderate* (primary patency loss) Low (AVF dialysis suitability, interventions to maintain patency or assist maturation [AVF/AVG], arteriovenous access abandonment, gastrointestinal adverse effects, hospitalization) Very low (bleeding, all-cause mortality, cardiovascular mortality)	Weak [5]
Statins	Patients may reasonably choose not to take statins to improve arteriovenous access patency based on very low certainty that treatment makes little or no difference to AVF failure, primary or secondary arteriovenous access patency.	*Very low*	Weak [6]
ACEI/ARB	Patients with an arteriovenous access may reasonably choose not to take an ACEI or ARB based on the absence of randomized controlled trial evidence to support their potential benefits in improving primary or secondary arteriovenous patency.	*Not graded*	Very weak [7–11]
Calcium channel blockers	Patients with an arteriovenous access may reasonably choose not to take a CCB based on the absence of randomized controlled trial evidence to support their potential benefits in improving primary or secondary arteriovenous patency.	*Not graded*	Very weak [12, 13]
Infrared therapy	We suggest far infrared therapy can be used in AVF to improve primary patency and assisted patency, and reduce surgical interventions for AVF dysfunction.	*Not graded*	Weak [14]

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Table 44.1 (Continued)

Treatment	Recommendation	Certainty of evidence	Strength of recommendation
PRT-201 elastase	Patients undergoing arteriovenous access creation may reasonably choose not to have local application of PRT-201 elastase based on the absence of randomized controlled trial evidence to support their potential benefits in improving access patency.	*Not graded*	Very weak [15–17]
Endothelial loaded gel foam wrap (Vascugel)	Patients with an arteriovenous access may reasonably choose not to have Vascugel applied at time of AVF creation based on the absence of randomized controlled trial evidence to support their potential benefits in improving access patency.	*Not graded*	Very weak [18]
Paclitaxel-coated balloons	Patients with AVF stenosis may choose not to undergo revascularization with paclitaxel-coated balloon angioplasty based on the absence of high-quality, large-scale randomized controlled trial evidence.	*Not graded*	Weak [19]
Local application of sirolimus (COLL-R)	Patients undergoing arteriovenous access creation may reasonably choose not to have periadventitial application of R-COLL (a combination product of sirolimus and a collagen membrane) to improve arteriovenous access outcomes based on the absence of high-quality, large-scale randomized controlled trial evidence.	*Not graded*	Very weak [20]
Novel surgical techniques	Patients undergoing AVF creation may reasonably choose not to have novel surgical techniques including the use of an Optiflow anastomotic device or a piggybacking straight-line onlay technique based on the absence of randomized controlled trial evidence to support their efficacy.	*Not graded*	Very weak [21–23]
Endovascular arteriovenous fistula creation	Patients may reasonably choose not to undergo endovascular arteriovenous fistula creation based on the absence of randomized controlled trial evidence to support the superiority of this technique over open surgical access creation.	*Not graded*	Weak [24]
Central venous catheters			
Alterative anticoagulant locking solutions	Patients may reasonably choose not to use alterative anticoagulant locking solutions to prevent CVC thrombosis. We suggest that alternative anticoagulant locking solutions should be used to prevent CVC bacteremia. Antibiotic-based solution may be superior to nonantibiotic solutions.	*Low* (CVC thrombosis) *Moderate* (CVC bacteremia)	Weak [25]
Topical interventions to exit site	We suggest that topical interventions to the exit site should be used to prevent CVC bacteremia.	*Low*	Very weak [26]

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II type I receptor blocker; AVF, arteriovenous fistula; AVG, arteriovenous graft; CCB, calcium channel blocker.
GRADE assessment of the certainty of the evidence [27]: High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different* is low. Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different* is moderate. Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different* is high. Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different* is very high. **Substantially different = a large enough difference that it might affect decision-making*.
[a] GRADE assessment not available in original publications, GRADE assessment performed by authors of this chapter.

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affect successful AVF/AVG placement such as a history of peripheral and/or central venous cannulation and pacemaker insertion. Likewise a detailed clinical examination is extremely important, including evaluation of the arterial and venous system in both upper limbs, neck, and chest [79].

In addition to a clinical evaluation, preoperative assessment of the venous and arterial system in the arms has been recommended as an adjunct to assist the surgeon in selecting the best site for access formation and therefore improve AVF/AVG suitability [31]. Table 44.2 summarizes findings from randomized trials comparing ultrasound preoperative assessment to a standard clinical assessment on AVF creation, maturation and usability for hemodialysis [1]. Despite the widespread practice of ultrsound preoperative vein mapping, the evidence that this practice improves AVF outcomes is uncertain largely due to the small sample sizes and the number of trials. Current trial data suggest that the use of ultrasound at best modestly improves AVF maturation and usability by about 12% over a standard clinical assessment.

Vascular Access Surveillance

Once permanent vascular access has been established, the major clinical goal is to prevent complications, principally vascular stenosis resulting in failure (thrombosis) of the AVF or AVG. The ability to prevent AVF and AVG failure is an important clinical goal as early elective repair can avoid interruption to dialysis. The distinction between monitoring and surveillance of the vascular access is important. Vascular access monitoring refers to regular physical examination of the AVF or AVG by inspection, palpation and auscultation to detect physical signs of access dysfunction. Vascular access surveillance refers to the periodic evaluation of the vascular access by means of specialized tests that involve special instrumentation which includes the assessment of dynamic venous pressure (DVP) and static venous pressure (SVP), vascular access recirculation, doppler ultrasound (DU) screening, and vascular access blood flow (Qa) measurement. Vascular access monitoring and surveillance are complementary techniques.

Regular physical examination plays an important role in the management of the hemodialysis patient and is the most important first step in the assessment of the AVF/AVG [79]. Assessment of the pulse, thrill/bruit, and clinical features together with the arm elevation test and pulse augmentation demonstrate reasonable sensitivity and specificity for the detection of inflow and outflow AVF stenosis [80, 81]. Physical findings suggesting a significant venous stenosis include edema of the access extremity, prolonged bleeding post venipuncture, and changes in the physical characteristics of the pulse or thrill. Physical examination has excellent specificity to detect central venous stenosis but sensitivity is poor [80]. Coexistent inflow and outflow stenosis are also poorly detected by physical examination [80].

Vascular Access Surveillance: Access Blood Flow Monitoring

The most commonly used surveillance technique is the measurement of access blood flow. Vascular access blood

Table 44.2 Summary of findings: use of pre-operative imaging prior to AVF formation.

Outcomes	No. of participants (no. of studies)	Absolute effect per 1000 patients treated for 1 year (95% CI)	Relative risk (95% CI)	Certainty of the evidence (GRADE)	Conclusion
Pre-operative Ultrasound imaging vs. standard assessment					
AVF created	433 (4)	51 more (43 fewer to 154 more)	1.06 (0.95–1.18)	Very low ●○○○	It is uncertain whether pre-operative ultrasound imaging increases AVF creation
Mature AVF	356 (3)	78 more (14 fewer to 176 more)	1.11 (0.98–1.25)	Low ●●○○	It is uncertain whether pre-operative ultrasound imaging increases AVF maturation
AVF used for dialysis	286 (2)	86 more (7 fewer to 200 more)	1.12 (0.99–1.28)	Low ●●○○	It is uncertain whether pre-operative ultrasound imaging increases AVF usability

CI, confidence interval.
Treatment estimates are drawn from Kosa et al. [1]. GRADE assessment of the certainty of the evidence [27]: High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different* is low. Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different* is moderate. Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different* is high. Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different* is very high. **Substantially different = a large enough difference that it might affect decision-making*.

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flow can be measured by indicator dilution techniques or by estimating Qa most commonly using Doppler ultrasound [31]. Prospective studies, including one randomized trial [82], have sought an association between Qa and the risk of thrombosis and/or the presence of stenosis [82–87]. AVGs are at risk of thrombosis at higher flows (cut off 500–750 ml/min) [84, 85] and AVFs at lower flows (300–500 ml/min), which makes comparisons difficult [87]. However, for vascular access surveillance to be successful the individual screening tests must be efficient at detecting the presence of an underlying significant stenosis, and any pre-emptive correction of a stenosis thus detected should result in a reduction in access thrombosis rates and prolong access survival.

Trials assessing vascular access surveillance with pre-emptive correction of the vascular access stenosis have recently been summarized [2]. This Cochrane review included all trials assessing active surveillance, irrespective of the technique, with comparison to usual clinical monitoring. Results are summarized in Table 44.3. Overall there were 14 studies, including a total of 1212 participants. The most commonly used surveillance technique was the measurement of Qa by either ultrasound dilution or Doppler ultrasound. Study sample size was small and in general the risk of bias was high or unclear in the majority of included studies. Flow thresholds used for the triggering of investigation also varied between the studies. When assessing the effect of surveillance on access thrombosis for both AVG and AVF there is a suggestion for a modest 19% reduction in the risk of thrombosis (relative risk [RR] 0.79, 95% confidence interval [CI] 0.65, 0.97). When AVF and AVG were assessed separately the reduction in thrombosis rate was

Table 44.3 Summary of findings: access surveillance.

Outcomes	No. of participants (no. of studies)	Absolute effect per 1000 patients treated for 1 year (95% CI)	Relative risk (95% CI)	Certainty of the evidence (GRADE)	Conclusion
Access surveillance with pre-emptive correction (comparator clinical dysfunction)					
Access loss (assisted patency): AVF and AVG combined	972 (11)	54 fewer (98 to 3 fewer)	0.80 (0.64–0.99)	Low ●●○○	It is uncertain if surveillance of AVF/AVG with pre-emptive correction reduces AVF/AVG loss
Access loss (assisted patency): AVG only	662 (7)	91 fewer (218 fewer to 77 more)	0.87 (0.69–1.11)	Moderate ●●●○	It is probable that surveillance of AVG with pre-emptive correction does not reduce AVG loss
Access loss (assisted patency): AVF only	310 (4)	110 fewer (157 to 31 fewer)	0.50 (0.29–0.86)	Low ●●○○	It is possible that surveillance of AVF with pre-emptive correction reduces AVF loss
Access thrombosis (unassisted patency): AVF and AVG combined	1212 (18)[a]	74 fewer (123 to 11 fewer)	0.79 (0.65–0.97)	Low ●●○○	It is possible that surveillance of AVF/AVG with pre-emptive correction reduces AVF/AVG thrombosis
Access thrombosis (unassisted patency): AVG only	697 (11)	20 fewer (82 fewer to 49 more)	0.95 (0.80–1.12)	Moderate ●●●○	It is probable that surveillance of AVG with pre-emptive correction does not reduce AVG thrombosis
Access thrombosis (unassisted patency): AVF only	515 (7)	139 fewer (181 to 81 fewer)	0.50 (0.35–0.71)	Low ●●○○	It is possible that surveillance of AVF with pre-emptive correction reduces AVF thrombosis
Catheter use	394 (6)	NA	0.58 (0.35–0.98)	Low ●●○○	It is possible that access surveillance reduces CVC use
Mortality	386 (5)	59 more (14 fewer to 173 more)	1.38 (0.91–2.11)	Low ●●○○	It is uncertain if access surveillance reduces mortality

CI, confidence interval; NA, not available.
Treatment estimates are drawn from Ravani et al. [2]. GRADE assessment of the certainty of the evidence [27]: High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different* is low. Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different* is moderate. Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different* is high. Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different* is very high. **Substantially different = a large enough difference that it might affect decision-making.*
[a] 18 comparisons in 13 studies.

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confined to studies assessing AVF (RR 0.50, 95% CI 0.50, 0.71) while no effect was seen in those assessing AVG (RR 0.95, 95% CI 0.80, 1.12). Similarly, when the more important endpoint of access loss was examined, there was again a suggestion of a modest reduction in access loss with surveillance for AVF/AVG combined which was driven by a beneficial effect seen in AVF than was not evident in AVG. While the data suggest a potential benefit for access surveillance in relation to AVF loss, the results should be tempered by the fact that conclusions are based on only four studies with a small overall sample size, translating into a low certainty in the evidence. Finally, six studies also assessed the effect of surveillance on subsequent catheter use and suggested a reduction in catheter use in patients randomized to the surveillance arm.

Vascular Access Surveillance: Other Screening Techniques

Numerous other techniques have been advocated, including the measurement of access recirculation (AR), and dynamic and/or SVPs. AR reduces dialysis efficiency and occurs when the dialyzed blood, returning via the venous needle of the extracorporeal circuit, is taken up again through the arterial needle. This leads to bypassing of the systemic circulation and occurs within the AVG or AVF, when Qa is less than the dialyser blood flow (Qb) [88]. Thus, the presence of AR signifies reduced Qa resulting from the presence of a hemodynamically significant stenosis. The clinical usefulness of AR measurements in AVG surveillance is limited as the risk of thrombosis in AVG is high once Qa is reduced to 500–800 ml/min, a range of blood flow which is too high to cause AR [33]. Unlike AVG, AVF blood flow can decrease to lower than prescribed dialyzer blood flow while still maintaining patency. Thus, the measurement of AR can be a useful tool to detect AVF stenosis although there have been no randomized trials performed to date. However, measurement of AR using saline dilution failed to detect a significant number of patients with documented low AVF blood flow and thus does not add any extra benefit to Qa monitoring [86, 89, 90].

Pressure within AVGs and AVFs can be considered as a surrogate of blood flow but the relationship between pressure and flow differs between them (reviewed in [91]). Pressure is measured either at the venous drip chamber during dialysis (DVP) or with the blood pump stopped (SVP) using standardized methods [33, 92]. Schwab et al. [93] first described an association between raised DVP and the presence of AVG stenosis at the venous anastomosis and subsequently developed a screening/monitoring protocol [94]. Serial measurements should be performed, with the trend being more important than single values, remembering that any lesions within the body of an AVG will not be detected if proximal to the venous needle [95]. Given the problems associated with measuring venous drip chamber pressure, Besarab et al. suggested the measurement of intra-access pressure [95, 96]. While demonstrating a reduction in the thrombosis rate using historical controls [96], at present no randomized controlled trial (RCT) of either dynamic or intra-access pressure measurements in AVG or AVF has been performed [92]. An RCT of SVP monitoring versus clinical evidence of access dysfunction in AVG did not demonstrate a benefit of screening using SVP with angioplasty on AVG survival [97]. While venous pressure monitoring is widely practiced, the evidence that the detection and treatment of a significant stenosis in AVG prolongs graft survival is of poor quality [92]. Since the presence of collaterals prevents the rise in venous pressure consequent on a reduction in Qa due to a stenosis, DVP is not recommended as a surveillance technique to detect significant stenosis in AVF although for upper arm AVF this may not be the case where there is predominantly one draining vein.

Treatment

Prevention of Arteriovenous Access Failure

The main goal of treating arteriovenous access failure is to maintain access patency by preventing stenosis and thrombosis formation. In newly formed AVF and to a lesser extent AVG, an additional treatment target is the successful maturation of the access characterized by achievement of an adequate caliber, wall strength, and blood flow to resist repeated cannulation and achieve prescribed hemodialysis.

Recent advantages in the understanding of the biology of access maturation and the pathophysiology of vascular access dysfunction/failure (Figure 44.2) have helped to develop novel treatment targets and interventions to establish and maintain a functional arteriovenous access. These interventions can be classified into (i) systemic medical therapies including antiplatelet agents, omega-3 polyunsaturated fatty acid (fish oils), statins, inhibitors of the renin-angiotensin-aldosterone system (RAAS), and calcium channel blockers (CCB) and (ii) local treatment approaches such as novel surgical techniques, minimally invasive AVF creation, far infrared therapy, perivascular application of recombinant elastase, endothelial loaded gel foam wrap (Vascugel), and antiproliferative agents such as sirolimus (Coll-R) and paclitaxel-coated balloon angioplasty. Most of these interventions are multitargeted with pleotropic effects on flow dynamics and the vascular biology (Box 44.2) [98]. Despite multiple treatment strategies, most of the benefits are limited to the reduction of early thrombosis and patency loss, while high-quality evidence

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Box 44.2 Treatment Strategies to Improve Arteriovenous Access Function

Systemic medical interventions	Effects on vascular biology/hemodynamics
Antiplatelet agents – Aspirin – Thienopyridines (e.g. clopidogrel, ticlopidine) – Dipyridamole – Sulfinpyrazone – Picotamide	Antiaggregatory Anti-inflammatory Antiproliferative
Omega-3 polyunsaturated fatty acids (fish oils)	Antiaggregatory Vasodilatory Inhibition of smooth muscle cell proliferation Reduction in blood viscosity Anti-inflammatory, resolution of inflammation Improved cardiovascular health
Statins	Anti-inflammatory Antiaggregatory Vasodilation Inhibition of smooth muscle cell proliferation Improved cardiovascular health
RAAS inhibitors – Angiotensin converting enzyme inhibitors – Angiotensin II type I receptor blockers	Inhibition of smooth muscle cell proliferation Antiaggregatory Vasodilation
Calcium channel blockers	Vasodilation Inhibition of neointimal hyperplasia
Local interventions	
Novel surgical techniques – Piggybacking straight-line onlay technique (pSLOT)	Optimizing flow and shear stress
– Optiflow device	Optimizing flow and shear stress by fixation of anastomotic angle of AVF at 60° Shielding of peri-anastomotic region
Endovascular AVF creation using radiofrequency magnetic catheter-based system	Reduction in vessel trauma and resulting triggers for neointimal hyperplasia formation
Far infrared therapy	Inhibition of vascular smooth muscle cell proliferation Inhibition of platelet aggregation Vasodilation Reduction in oxidative stress
Perivascular application of recombinant elastase Human type 1 pancreatic elastase (PRT-201)	Vasodilation by fragmentation of elastin in blood vessel wall Inhibition of adventitial myofibroblast migration to the intima
Endothelial loaded gel foam wrap (Vascugel)	Inhibition of thrombus formation Reduction in negative remodeling (inward) following vascular injury by reducing matrix metalloproteinase-2 expression, neovascularization, and adventitial fibrosis)
Antiproliferative agents – COLL-R (drug-eluted combination product of collagen membrane and sirolimus) – Paclitaxel-coated balloon angioplasty	Inhibition of vascular smooth muscle cell proliferation

Source: Based on Viecelli AK, Mori TA, Roy-Chaudhury P, et al. (2018)

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to demonstrate long-term benefits for clinically meaningful outcomes such as the usability of an AVF or AVG are largely absent.

Systemic Medical Interventions

Antiplatelet Agents

Antiplatelet agents are expected to reduce patency loss of AVF and AVG predominantly via an antithrombotic effect. Individual agents may have additional inhibitory actions on smooth muscle cell proliferation (e.g. dipyridamole) and inflammation (e.g. aspirin), with the potential to reduce neointimal hyperplasia, stenosis, and thrombosis formation [98, 99]. Based on a meta-analysis of 21 RCTs of any type of antiplatelet agent (summarized in Table 44.4) [3], the benefits of antiplatelet therapies are restricted to reducing the risk of early thrombosis and patency loss of AVFs, while their benefit remains uncertain for AVGs. There is insufficient evidence to determine the longer-term benefits of antiplatelet agents on arteriovenous access suitability for hemodialysis, the need for access interventions or their safety, particularly the risk of bleeding. Treatment benefits of individual anti-

Table 44.4 Summary of findings: antiplatelet therapies[a].

Outcomes	No. of participants (no. of studies)	Absolute effect per 1000 patients treated for 1 year (95% CI)	Relative risk (95% CI)	Certainty of the evidence (GRADE)	Conclusion
Arteriovenous access failure (thrombosis or loss of patency)					
AVF	1242 (6)	NA	0.49 (0.30–0.81)	Moderate ●●●○	Antiplatelet agents probably decrease AVF failure
AVG	956 (3)	NA	0.94 (0.80–1.10)	Moderate ●●●○	Antiplatelet agents probably make no difference to AVG failure
Early access thrombosis (before 8 weeks)					
AVF	1105 (5)	NA	0.43 (0.26–0.73)	Moderate ●●●○	Antiplatelet agents probably decrease early AVF thrombosis.
AVG	16 (1)	NA	Not estimable	Absent	NA
Failure to attain suitability for dialysis					
AVF	794 (2)	NA	0.57 (0.13–2.51)	Low ●●○○	It is uncertain whether antiplatelet agents reduce AVF dialysis suitability
AVG	649 (1)	NA	0.51 (0.16–1.68)	Low ●●○○	It is uncertain whether antiplatelet agents reduce AVG dialysis suitability
Need for arteriovenous access intervention					
AVF	866 (1)	NA	0.69 (0.26–1.83)	Low ●●○○	It is uncertain whether antiplatelet agents reduce the need for AVF interventions
AVG	649 (1)	NA	0.89 (0.64–1.25)	Low ●●○○	It is uncertain whether antiplatelet agents reduce the need for AVG interventions
Major bleeding	3930 (11)	NA	0.93 (0.58–1.49)	Low ●●○○	It is uncertain whether antiplatelet agents cause major bleeding
Minor bleeding	237 (4)	NA	1.22 (0.51–2.91)	Low ●●○○	It is uncertain whether antiplatelet agents cause minor bleeding

AVF, arteriovenous fistula; AVG, arteriovenous graft; CI, confidence interval; NA, not available.
Treatment estimates are drawn from one systematic review and meta-analysis (Palmer et al. [3]). GRADE assessment of the certainty of the evidence [27]: High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different* is low. Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different* is moderate. Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different* is high. Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different* is very high. **Substantially different = a large enough difference that it might affect decision-making.*
[a] Antiplatelet agents include aspirin, ticlopidine, dipyridamole, dipyridamole and aspirin combined, clopidogrel, sulfinpyrazone, picotamide, clopidogrel, and aspirin.

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platelet agents has been assessed in a Cochrane review published in 2015 [4]. With the exception of low-quality evidence to support the use of ticlopidine to reduce early AVF thrombosis (three trials, 239 participants, odds ratio [OR] 0.45, 95% CI 0.25–0.82), there was insufficient evidence to determine whether other antiplatelet agents were effective in preventing arteriovenous access failure [4]. A recently published RCT of fish oil supplementation and aspirin use in patients undergoing AVF creation showed that 100 mg of aspirin given to a subgroup of 388 participants for 3 months did not reduce the composite primary outcome of AVF failure at 12 months (RR 1.05, 95% CI 0.84–1.31) [40]. Similarly, no treatment benefit was seen for the individual outcome components in the composite AVF failure outcome, including AVF thrombosis (RR 1.09, 95% CI 0.72–1.64), AVF abandonment (RR 1.31, 95% CI 0.89–1.95), and cannulation failure (RR 0.99, 95% CI 0.76–1.27) [40]. In summary, these data suggest that antiplatelet agents may be used to prevent early thrombosis and patency loss but longer-term benefits on access patency and usability remain uncertain.

Omega-3 Polyunsaturated Fatty Acids (Fish Oils)

Omega-3 polyunsaturated fatty acids inhibit platelet aggregation [100] and exert anti-inflammatory [101, 102], antiproliferative [103, 104], and vasodilatory effects [105] on vascular structures. The evidence for fish oil supplementation to reduce arteriovenous access failure has been summarized in a recent systematic review and meta-analysis (Table 44.5) [5]. Moderate certainty evidence suggests that fish oil supplementation prevents primary arteriovenous patency loss, but fish oil has little or no effect on dialysis suitability failure, arteriovenous access abandonment or need for interventions, based on low-level evidence. The risks of treatment-related bleeding or gastrointestinal side effects are uncertain.

Statins

The pleiotropic effects of statins on the vasculature outlined in Box 44.2 may reduce arteriovenous access stenosis and thrombosis [106, 107]. The clinical evidence for statin effects on arteriovenous access failure is restricted to observational trial data and post hoc analyses of RCTs. A post hoc analysis of 2352 participants from the Study of Heart and Renal Protection (SHARP) trial suggested a 13% reduction in vascular access occlusive events in participants treated with simvastatin plus ezetimibe compared to placebo while this benefit was not found in a second post hoc analysis of a RCT of similar size using rosuvastatin [108]. Several other retrospective analyses did not support the use of statins to improve primary or secondary arteriovenous access patency [109], access maturation [110], stenosis formation [111], time to recurrent angioplasties [111], or cumulative access survival (after excluding primary failure) [109, 110]. A recently published meta-analysis of six retrospective cohort studies and one small RCT of 90 participants demonstrated uncertain effects of statin use on AVF failure (seven studies, 20 126 participants, pooled RR 0.89, 95% CI 0.70–1.12) based on low-level evidence [6]. In summary, there is insufficient evidence to support the use of statin therapy for preventing arteriovenous access failure and larger, international RCTs to further explore this treatment option are needed.

Renin-Angiotensin-Aldosterone System Blockers (Angiotensin Converting Enzyme Inhibitors and Angiotensin II Type I Receptor Blockers)

Preclinical data suggests a vascular benefit of angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) via inhibition of intimal hyperplasia formation, platelet activation, and adhesion as well as promoting vasodilation [112–116]. Clinical evidence for ACEI/ARB use is confined to cohort studies and large registry analyses with conflicting results regarding benefits on primary and secondary arteriovenous access patency. Data interpretation is limited by the large variations in treatment agents, dose and duration, outcome definitions, study populations, and unadjusted confounding inherent to observational studies [7–11]. Additional evidence from RCTs will be required to ascertain potential benefits of using ACEIs/ARBs to improve arteriovenous access outcomes.

Calcium Channel Blockers

Calcium channel blockers (CCBs) may promote arteriovenous access maturation and reduce (re-)stenosis via vasodilation and inhibition of neointimal hyperplasia [12, 13, 117, 118]. No RCT has been performed to assess the effect of CCB on arteriovenous access outcomes. A large retrospective analysis of 42 244 participants (13 121 on CCB) suggests an association between CCB use and prolonged primary patency of AVFs (hazard ratio [HR] 0.485, 95% CI 0.44–0.50) and AVGs (HR 0.48, 95% CI 0.44–0.53) [11]. This association was only evident in AVG but not in AVFs in another smaller retrospective study of 2312 participants of whom 970 were on CCBs [109].

Local Treatment Strategies

Far Infrared Therapy

Far infrared radiation (FIR), an invisible electromagnetic wave applied locally over the skin, has been shown to inhibit vascular smooth muscle cell proliferation and platelet aggregation, promote vasodilation, improve endothelial function, and reduce oxidative stress [119–121]. A meta-analysis of four RCTs in FIR to improve AVF outcomes is summarized

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Table 44.5 Summary of findings: omega-3 polyunsaturated fatty acid (fish oil) supplementation.

Outcomes	No. of participants (no. of studies)	Absolute effect per 1000 patients treated for 1 year (95% CI)	Relative risk (95% CI)	Certainty of the evidence (GRADE)	Conclusion
Primary patency failure (AVF and AVG combined)	761 (3)	73 fewer (123 to 8 fewer)	0.81 (0.68–0.98)	Moderate ●●●○	Fish oil probably prevents primary arteriovenous access patency loss
AVF		NA		NA	
AVG		NA		NA	
AVF dialysis suitability failure	536 (1)	15 fewer (82 fewer to 70 more)	0.95 (0.73–1.23)	Low ●●○○	It is uncertain whether fish oil supplementation reduces dialysis suitability failure of newly created AVF
Interventions to maintain patency or assist maturation (AVF and AVG combined)	732 (2)	50 fewer (99 fewer to 11 more)	0.82 (0.64–1.04)	Low ●●○○	It is uncertain whether fish oil supplementation reduces the need for interventions to maintain patency or assist maturation of AVF and AVG
AVF	536 (1)	NA	0.87 (0.61–1.25)	NA	
AVG	196 (1)	NA	0.78 (0.56–1.07)	NA	
Access abandonment (AVF and AVG combined)	732 (2)	56 fewer (105 fewer to 8 more)	0.78 (0.59–1.03)	Low ●●○○	It is uncertain whether fish oil supplementation reduces arteriovenous access abandonment
AVF	536 (1)	NA	0.87 (0.62–1.21)	NA	
AVG	196 (1)	NA	0.64 (0.41–1.01)	NA	
Bleeding	794 (4)	18 more (10 fewer to 68 more)	1.40 (0.78–2.49)	Very low ●○○○	It is uncertain whether fish oil supplementation increases the risk of bleeding
GI adverse effects	816 (4)	12 more (20 fewer to 76 more)	1.22 (0.64–2.34)	Low ●●○○	It is uncertain whether fish oil supplementation increases gastrointestinal side effects
All-cause mortality	799 (4)	1 fewer (21 fewer to 37 more)	0.98 (0.51–1.86)	Very low ●○○○	It is uncertain whether fish oil supplementation reduces all-cause mortality
Cardiovascular mortality	768 (4)	17 fewer (29 fewer to 13 more)	0.55 (0.22–1.35)	Very low ●○○○	It is uncertain whether fish oil supplementation reduces cardiovascular mortality
Hospitalization	574 (2)	4 fewer (72 fewer to 84 more)	0.99 (0.81–1.22)	Low ●●○○	It is uncertain whether fish oil supplementation reduces hospitalization

AVF, arteriovenous fistula; AVG, arteriovenous graft; CI, confidence interval; GI, gastrointestinal; NA, not available.
Treatment estimates are drawn from one systematic review and meta-analysis (Viecelli et al. [5]). GRADE assessment of the certainty of the evidence [27]: High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different* is low. Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different* is moderate. Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different* is high. Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different* is very high. **Substantially different = a large enough difference that it might affect decision-making*.

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in Table 44.6 [14]. Applying FIR for 40 minutes during each hemodialysis session had a beneficial effect on unassisted and assisted patency as well as intervention. A second meta-analysis published in 2017 [122] reported additional benefits on surrogate markers including mean blood flow (10 studies, 864 participants, mean change 82 ml/min, 95% CI 46–117), AVF diameter (five studies, 381 participants, 0.36 mm, 95% CI 0.22–0.51), and reduction in needling pain (three studies, RR 0.08, 95% CI 0.06–0.10). The quality of evidence is limited by small-scale studies (32–280 patients) of relatively short duration (maximum 12 months) with limited external validity, largely unknown or high risk of study bias and significant heterogeneity [14, 122]. Given the convenience of FIR application during dialysis sessions and its non-invasive nature, well-designed, international, multicenter RCTs of longer follow-up duration are warranted.

Novel Surgical Techniques

Surgical techniques have been developed to optimize flow dynamics at the site of the anastomosis with the intension of reducing endothelial dysfunction and the downstream vasoconstrictive, prothrombotic, and inflammatory cascade that follows [66, 123]. A sutureless vascular anastomotic device called Optiflow has been developed to maintain an optimal angle of 60° between artery and vein to optimize flow patterns and shear stress as well as shielding the perianastomotic region to prevent stenosis formation. Feasibility and safety were demonstrated in a small pilot study [23]. A prospective study of 41 patients undergoing AVF creation demonstrated promising 42- and 90-day maturation (72% and 68%) as well as primary unassisted patency rates (88% and 78%) [22]. Similarly, the use of the piggybacking straight-line onlay technique may reduce AVF failure compared to the traditional end-to-side and side-to-side straight-line onlay techniques [21]. However, there are currently no RCTs to confirm potential treatment benefits of these novel surgical techniques.

Endovascular Arteriovenous Fistula Creation

The endovascular creation of an AVF using a radiofrequency magnetic catheter-based system may cause less vessel trauma compared to open surgical creation, thereby reducing downstream stimuli for neointimal hyperplasia and stenosis formation [124]. Using this minimally invasive technique in a prospective, single-arm, multicenter study of 80 participants resulted in 98% successful AVF creation and 87% (95% CI 75–94%) physiological maturation within 3 months (brachial artery flow ≥500 ml/min and vein diameter ≥4 mm) [24]. Sixty-four percent (95% CI 48–78%) of participants were able to receive prescribed hemodialysis through the AVF using two-needle cannulation with an intervention rate of 0.46/patient-year. Primary patency at 12 months was 69% (95% CI 54–79%) and cumulative patency 84% (95% CI 71–91) [24]. Comparing this technique to surgical AVF creation in an RCT may be difficult due to the unique location and type of vessels used for endovascular AVF creation and the inability to blind the treatments.

Local Application of Antiproliferative Agents

Antiproliferative agents including sirolimus (rapamycin) and paclitaxel applied locally either around the adventitial surface (e.g. COLL-R, a combination product of siroli-

Table 44.6 Summary of findings: far infrared therapy.

Outcomes	No. of participants (no. of studies)	Absolute effect per 1000 patients treated for 1 year (95% CI)	Relative risk (95% CI)	Certainty of the evidence (GRADE)	Conclusion
Primary AVF patency	610 (4)	137 more (60 to 221 more)	1.23 (1.12–1.35)	Very low ●○○○	Infrared therapy may increase primary patency of AVF
Assisted AVF patency (following salvage procedure for dysfunctional AVF)	300 (2)	94 more (34 more to 163 more)	1.11 (1.04–1.19)	Very low ●○○○	Infrared therapy may increase assisted primary patency of AVF
Surgical interventions for AVF dysfunction	249 (2)	93 less (137 to 9 less)	0.49 (0.25–0.95)	Very low ●○○○	Infrared therapy may reduce surgical interventions for AVF

AVF, arteriovenous fistula; AVG, arteriovenous graft; CI, confidence interval; GI, gastrointestinal; NA, not available.
Treatment estimates are drawn from one systematic review with meta-analysis (Bashar et al [14]). GRADE assessment of the certainty of the evidence [27]: High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different* is low. Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different* is moderate. Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different* is high. Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different* is very high. **Substantially different = a large enough difference that it might affect decision-making*.

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mus and a collagen membrane) or endoluminal during balloon-angioplasty (e.g. paclitaxel-coated balloon) can reduce vascular smooth muscle cell proliferation and neointimal hyperplasia formation, thereby preventing (re-)stenosis [125]. Following promising results on AVG patency from a single-arm phase II study using COLL-R in 12 hemodialysis patients [20], the results from a phase III RCT using COLL-R to improve AVF hemodialysis suitability is currently awaited (NCT02513303). Similarly, the use of paclitaxel-coated balloon angioplasty to treat AVF stenosis has shown beneficial effects on revascularization-free survival compared to high pressure balloon angioplasty in a small single-center RCT [19], but multicenter, large-scale RCTs are currently lacking to provide certainty on the treatment benefits of these treatment approaches.

Perivascular Application of Recombinant Elastase

Recombinant human type-1 pancreatic elastase (PRT-201) applied locally during arteriovenous access creation is used to fragment elastin with the premise to promote vasodilation and inhibit migration of adventitial myofibroblasts into the intimal layer [15, 98]. An immediate effect of high-dose PRT-201 on intraoperative vein outflow diameter and blood flow has been shown in an RCT of 89 patients undergoing AVG creation [17], yet clinically meaningful long-term effects on unassisted primary patency within the first year of access creation have not been found in an RCT of 151 patients undergoing AVF creation [16].

Endothelial-loaded Gel Foam Wrap (Vascugel)

Vascugel is an endothelial-cell-loaded wrap containing allogeneic aortic endothelial cells to promote outward vascular remodeling and prevent neointimal hyperplasia [18, 125]. Despite promising preclinical studies to support endothelial-mediated beneficial effects [126, 127] and a phase I/II trial to confirm the safety of this procedure [18], there is currently no phase III RCTs available to further explore this local treatment approach.

In summary, there is moderate certainty evidence to suggest a short-term benefit of anti-platelet therapies to improve AVF patency and of fish oil supplementation to improve arteriovenous patency within the first 12 months of access creation. Low to very low certainty evidence supports to use of FIR therapy applied during dialysis to improve AVF maturation, patency, and reduce needling pain. Novel local treatment approaches, including novel surgical techniques, minimally invasive endovascular AVF creation, and local application of antiproliferative agents, will require further study in well-designed, international RCTs to increase the certainty of the evidence.

Prevention of Arteriovenous Access Failure

Prevention and Treatment of CVC Malfunction

With the widespread use of cuffed CVCs in hemodialysis patients, the prevention of complications related to their use has become a major focus. The two principle CVC complications are CVC malfunction, which is principally due to catheter-related thrombosis, and CVC-related bacteremia, which is discussed in the next section. Catheter-related thrombosis is a common problem and is classified as either extrinsic where thrombus forms outside the catheter or intrinsic with thrombus forming inside the catheter [128]. Causes of extrinsic thrombi include central vein thrombosis, intra-atrial thrombus, and cardiac mural thrombus. Intrinsic thrombus may be intraluminal, attached to the catheter tip or surround the catheter – formation of a fibrin sheath [128].

Strategies tested to prevent CVC thrombosis have generally assessed newer novel anticoagulant agents, thrombotic agents or a systematically administered agent. Results of the two Cochrane reviews are summarized in Table 44.7 [25, 129]. Currently the newer novel anticoagulant agents do not offer any advantage over conventional heparin locks regarding CVC thrombosis, although they may offer advantages for other outcomes such as bacteremia, as discussed below. Likewise, systemic agents such as warfarin are also no more effective than standard heparin lock.

Interventions aimed at treating CVC thrombosis and malfunction include Instillation of thrombolytic agents, systemic administration of thrombolytic agent, radiologic fibrin sheath stripping +/- means with or without CVC guidewire exchange. Few randomized trials have been performed to guide specific recommendations. Instillation of a thrombolytic catheter lock likely are to be more effective than placebo [130] while fibrin sheath stripping may be as effective as thrombolytic therapy.

Prevention of Catheter-related Bacteremia

Catheter-related bacteremia is a major complication associated with CVC use, responsible for 70% of vascular access-related bacteremia in the United States [44], causing significant morbidity and mortality [43] as well as increased healthcare costs. Therefore, prevention of catheter-related bacteremia is an important treatment goal in the management of hemodialysis patients.

Trials addressing interventions aimed at reducing CVC-related bacteremia can be divided into three broad groups: those where the intervention is administered at the CVC exit site, those where antibiotic or antimicrobial is used as a catheter lock solution, and finally structural or

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Table 44.7 Summary of findings: CVC malfunction.

Outcomes	No. of participants (no. of studies)	Absolute effect per 1000 CVC days (95% CI)	Relative risk (95% CI)	Certainty of the evidence (GRADE)	Conclusion
Prevention of CVC thrombosis[a] (comparator heparin lock)					
Alternative anticoagulant locking solutions [129]	908 (9)	12 fewer (77 fewer to 77 more)	0.96 (0.74–1.26)	Very low ●○○○	There may be no difference between alternative anticoagulant locking solutions and heparin lock solutions in preventing CVC thrombosis
All antimicrobial locking solutions [25]	2080 (14)	NA	0.79 (0.52–1.22)	Very low ●○○○	There may be no difference between alternative antimicrobial locking solutions and heparin lock solutions in preventing CVC thrombosis
Antibiotic locking solutions only [25]	– (5)	NA	0.76 (0.42–1.38)	Very low ●○○○	It is uncertain whether any difference exists between antibiotic locking solutions and heparin lock solutions in preventing CVC thrombosis
Nonantibiotic antimicrobial locking solutions only [25]	– (8)	NA	0.85 (0.44–1.66)	Very low ●○○○	It is uncertain whether any difference exists between nonantibiotic antimicrobial locking solutions and heparin lock solutions in preventing CVC thrombosis
No/low-dose heparin lock [129]	123 (2)	2 fewer (15 fewer to 122 more)	0.90 (0.10–8.31)	Very low ●○○○	It is uncertain whether no/low-dose heparin prevents CVC thrombosis
Warfarin [129]	460 (5)	171 fewer (300 fewer to 96 more)	0.59 (0.28–1.23)	Very Low ●○○○	It is uncertain whether systemic warfarin prevents CVC thrombosis
rTPA lock [131]	225 (1)	146 fewer (219 fewer to 31 fewer)	0.58 (0.37–0.91)	Very low ●○○○	It is uncertain whether rTPA prevents CVC thrombosis
Mortality[a] (comparator heparin lock)[b]					
Alternative anticoagulant locking solutions [129]	1425 (8)	6 fewer (22 fewer to 21 more)	0.88 (0.54–1.43)	Very low ●○○○	It is uncertain whether alternative anticoagulant locking solutions reduce mortality
Warfarin [129]	403 (3)	16 fewer (45 fewer to 50 more)	0.78 (0.37–1.65)	Very low ●○○○	It is uncertain whether alternative anticoagulant locking solutions reduce mortality

CI, confidence interval; CVC, central venous catheter; NA, not available; rTPA = recombinant tissue plasminogen activator
Treatment estimates are drawn from three Cochrane reviews (Arechabala et al. [25] and Wang et al. [129]). GRADE assessment of the certainty of the evidence [27]: High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different* is low. Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different* is moderate. Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different* is high. Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different* is very high. **Substantially different = a large enough difference that it might affect decision-making.*
[a] Some studies included citrate combined with antibiotic.
[b] Some studies included citrate combined with antibiotic.

mechanical devices related or attached to the catheter to prevent infection.

Topical Interventions to the CVC Exit Site

Interventions applied to the cuffed CVC exit site aim to reduce CVC-related bacteremia by preventing bacterial skin growth and subsequent catheter colonization. Agents assessed in trials include mupirocin and polysorin antibiotic ointment, chlorhexidine impregnated dressings, and topical medi-honey. The most recent systematic review is now relatively out of date (published in 2010) and includes only studies assessing mupirocin, polysorin, and medi-honey (summarized in Table 44.8). The review suggests positive effects for the use of topical agents in reducing

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Table 44.8 Summary of findings: prevention of catheter related bacteremia.

Outcomes	No. of participants[a] (no. of studies)	Absolute effect per 1000 patients treated for 1 year (95% CI)	Relative risk (95% CI)	Certainty of the evidence (GRADE)	Conclusion
All antimicrobial locking solutions (comparator heparin lock)					
CVC-related bacteremia[b]: all catheters [25]	2994 (27)	NA	0.38 (0.27–0.53)	Low ●●○○	Antimicrobial solutions probably reduce the incidence of CVC-related bacteremia
CVC-related bacteremia[b]: tunneled catheters [25]	— (21)	NA	0.40 (0.30–0.53)	Low ●●○○	Antimicrobial solutions probably reduce the incidence of tunneled CVC-related bacteremia
CVC-related bacteremia[b]: nontunneled catheters [25]	— (6)	NA	0.37 (0.16–0.86)	Low ●●○○	Antimicrobial solutions probably reduce the incidence of nontunneled CVC-related bacteremia
Mortality [25]	— (—)	—	Not reported	Absent	Mortality not reported
Antibiotic locking solutions only (comparator heparin lock)					
CVC related bacteremia[b]: all catheters [25]	— (13)	NA	0.30 (0.22–0.42)	Low ●●○○	Antibiotic solutions probably reduce the incidence of CVC-related bacteremia
CVC-related bacteremia[b]: tunneled catheters [25]	— (9)	NA	0.30 (0.18–0.50)	Low ●●○○	Antibiotic solutions probably reduce the incidence of tunneled CVC-related bacteremia
CVC-related bacteremia[b]: nontunneled catheters [25]	— (4)	NA	0.14 (0.05–0.36)	Low ●●○○	Antibiotic solutions probably reduce the incidence of nontunneled CVC-related bacteremia
Nonantibiotic antimicrobial locking solutions only (comparator heparin lock)					
CVC-related bacteremia[b]: all catheters [25]	— (11)	NA	0.65 (0.41–1.05)	Low ●●○○	It is uncertain whether nonantibiotic antimicrobial locking solutions reduce the incidence of CVC-related bacteremia
CVC-related bacteremia[b]: tunneled catheters [25]	— (9)	NA	0.60 (0.40–0.91)	Low ●●○○	Nonantibiotic antimicrobial locking solutions probably reduce the incidence of tunneled CVC-related bacteremia
CVC-related bacteremia[b]: nontunneled catheters [25]	— (4)	NA	0.93 (0.48–1.81)	Low ●●○○	Nonantibiotic antimicrobial locking solutions probably make little or no difference to the incidence of nontunneled CVC-related bacteremia
Topical interventions to exit site					
CVC-related bacteremia[c] [26]	508 (5)	169 fewer (195 to 124 fewer)	0.26 (0.15–0.46)	Low ●●○○	Topical intervention may reduce the incidence of CVC-related bacteremia
CVC exit site infection [26]	346 (4)	160 fewer (182 to 110 fewer)	0.20 (0.09–0.45)	Low ●●○○	Topical interventions may reduce the incidence of CVC exit site infection
CVC removal [26]	379 (4)	139 fewer (160 to 107 fewer)	0.35 (0.25–0.50)	Low ●●○○	Topical interventions may reduce the need for CVC removal due to infection.
All-cause mortality [26]	322 (3)	85 fewer (116 to 9 more)	0.36 (0.12–1.07)	Low ●●○○	It is uncertain whether topical interventions reduce mortality

CI, confidence interval; CVC, central venous catheter; NA, not available.
Treatment estimates are drawn from two systematic reviews (Arechabala et al. [25] and McCann and Moore [26]). GRADE assessment of the certainty of the evidence [27]: High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different* is low. Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different* is moderate. Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different* is high. Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different* is very high. **Substantially different = a large enough difference that it might affect decision-making.*
[a] Number of subjects not reported for all outcomes in [25].
[b] Bacteremia rate per 1000 catheter days.
[c] Units not reported in review.

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rates of CVC bacteremia, exit site infection, and removal, but firm conclusions are difficult due to small sample size, the low quality of the included trials, and an unusually high rate of bacteremia in the some of the control groups. Since 2010, three trials assessing the use of chlorhexidine-impregnated dressings in hemodialysis have been reported. Rosenblum et al. in a large cluster RCT of 211 dialysis facilities assessed chlorhexidine application to the CVC exit site at each dialysis and dressing change showing a 41% reduction in CVC bacteremia [132]. Two small studies demonstrate conflicting results, with one showing no difference in bacteremia rates [133] while the other found significantly lower rates in the chlorhexidine-impregnated dressing group [134]. Finally, a recent systematic review assessing all CVCs (predominantly those in the intensive care unit setting but including three studies in hemodialysis patients) suggests there is moderate quality evidence that chlorhexidine-impregnated dressings reduce the frequency of catheter-related BSI per 1000 patient-days compared with standard polyurethane dressings (RR 0.51, 95% CI 0.33–0.78) [135].

Antimicrobial/Antibiotic Locking Solutions

Antimicrobial and antibiotic locking solutions are the best-studied interventions. These solutions are instilled into the catheter after every dialysis and aim to limit the formation of a biofilm which acts as a nidus for CVC-related bacteremia. Four systematic reviews have been published, two focusing on citrate-based locking solutions [129, 136] and one assessing antibiotic-based solutions with and without citrate [137]. The most recent (updated to include all studies to December 2017) included all antimicrobial solutions whether antibiotic or nonantibiotic based [25]. Table 44.8 summarizes the most recent review. Overall 39 individual trials (4216 subjects) were included, although only 30 trials (3392 subjects) could be incorporated into the meta-analysis. Overall study size was small and risk of bias in the majority uncertain or high for all domains except reporting bias. In all trials the comparator arm used a standard heparin catheter lock. Overall there is moderate certainty that the use of antimicrobial lock solutions results in a 55% reduction in the incidence of CVC-related bacteremia (Table 44.8). The beneficial effect remained consistent when assessed according to CVC type: tunneled or nontunneled. When assessed according to antibiotic and nonantibiotic antimicrobial solutions, the treatment effect strengthened in the case of antibiotic locks whereas for the nonantibiotic-based locks treatment estimates weakened and were not consistent. Mortality was not assessed in the majority of studies, making many any conclusions uncertain. Taurolidine has been assessed in two additional trials not included in the recent systematic review [138, 139]. Like the majority of previous studies both trials are limited by the small sample size (106 and 177 patients, respectively) while one reported catheter bacteremia in combination with catheter thrombosis, making any interpretation difficult [138], and the other compared taurolidine to a citrate-based solution [139].

Potential safety concerns in the use of antibiotic locks include concerns regarding drug-specific toxicity (e.g. gentamicin-induced ototoxicity [140]) and the emergence of antibiotic resistance [141, 142], while the use of high-dose citrate can potentially cause pulmonary embolism and fatal arrhythmias [143]. While it is clear that the use of an antimicrobial or antibiotic lock reduces CVC bacteremia, the optimal lock solution has yet to be determined. Only one trial [139] has compared the different locks against each other so whether or not an antimicrobial lock has advantages over an antibiotic-based lock is unknown and requires further study. Whether antimicrobial or antibiotic lock solutions are more effective than topical interventions to CVC exit site is also currently unknown; the rates of CRB are similar across the studies but no trials have compared them directly. Larger studies are also required to ascertain whether such interventions reduce mortality.

Structural or Mechanical Devices

Like the antimicrobial or antibiotic lock solutions, structural or mechanical devices related or attached to the catheter prevent infection by limiting the formation of a biofilm. The ClearGuard HD Antimicrobial Barrier Cap (Pursuit Vascular Inc.) is a chlorhexidine-coated catheter cap which dissolves into the lock solution proximal to the clamp. Two cluster randomized trials, both performed in 40 dialysis facilities with 2470 [144] and 627 [145] patients respectively, showed that compared to conventional dialysis caps, the bacteremia rates were lower in the intervention arms by 56% and 63%. Results were consistent across a number of subgroups, using stricter definitions of bacteremia, as well as reducing hospital admissions. Mortality was not reported in one of the studies [144] and was not different in the other although absolute numbers were very low (three total deaths only) [145]. Finally, one trial has compared a silver-coated to standard dialysis CVC and did not demonstrate any benefit [146]. Data for antibiotic-impregnated versus standard uncuffed general nondialysis catheters is summarized in Chapter 43.

Patient and Caregiver Treatment Preferences

Advances in hemodialysis vascular access care have been hindered by the significant heterogeneity of outcomes reported across trials that may be of limited relevance to

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end-users including patients and their caregivers. Standardized definitions for vascular access outcomes have been proposed by multiple working groups and initiatives [74, 147–151], yet the uptake in clinical trials has been minimal to date [152]. This issue is being addressed by the international Standardized Outcomes in Nephrology (SONG) initiative [153]. This initiative aims to establish and implement critically important outcomes (i.e. core outcomes sets) [154] across the spectrum of kidney disease that are based on the shared priorities of patients, caregivers, and health professionals. These core outcome sets are expected to be reported consistently in all trials of a specific area of research (e.g. hemodialysis, peritoneal dialysis, transplantation) to inform clinical practice in a reliable, consistent, and meaningful manner. For hemodialysis, the core outcomes identified include vascular access function, fatigue, cardiovascular disease, and all-cause mortality [155–157]. Based on the global input of patients, caregivers, health professionals, researchers, policy makers, and industry representatives, an outcome measure for vascular access function has been established and will be validated prior to its global implementation in hemodialysis research [156]. Consistent reporting of standardized outcome measures that are considered important not only by researchers but also by patients, caregivers, and clinicians is expected to advance future vascular access research to inform clinical practice in a meaningful way and improve patient-important outcomes.

Conclusion

Hemodialysis remains the dominant form of dialysis therapy for patients with ESKD and hence the provision and maintenance of vascular access for hemodialysis patients represents a management goal. Currently, the AVF remains the optimal vascular access for a majority of patients but not necessarily all patients. Of the strategies aimed at reducing primary AVF failure, antiplatelet agents and fish oils may be beneficial whereas statin and ACE/ARB therapy cannot currently be recommended. More recent novel therapies, such as infrared therapy and novel surgical techniques among others, require further investigation. Once established, AVF blood flow surveillance with pre-emptive stenosis correction reduces AVF thrombosis and may improve AVF loss. AVG blood flow surveillance with pre-emptive correction cannot be recommended. In patients dialyzing with a CVC, the alterative anticoagulant locking solutions (especially antibiotic-based solutions) reduce the incidence of CVC-related bacteremia and should be used. Alternatively, topical antimicrobial dressing applied the CVC exit site can also be considered to reduce the incidence of CVC-related bacteremia.

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Part 7

Peritoneal Dialysis

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Small Solute Clearance in Peritoneal Dialysis

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Introduction

The ideal method of assessing the adequacy of peritoneal dialysis (PD) has yet to be determined. Early studies attempting to quantify dialysis dose in hemodialysis (HD) patients used urea as a low molecular weight putative uremic toxin, eventually leading to the establishment of Kt/V_{urea} as a useful surrogate for small solute clearance [16, 17]. This term, Kt/V_{urea}, factors in several important parameters: clearance of urea (K), time on dialysis (t), and the urea distribution volume, or total body water (V). At the same time as the studies on Kt/V_{urea} were emerging in the HD literature, there was a relative paucity of data on quantification of the dose of PD, with only one group addressing kinetic modeling of peritoneal transport [18]. The data on Kt/V_{urea} in HD were therefore extrapolated to PD, with the addition of creatinine clearance (CrCl) as a complementary surrogate. While measures of solute clearance have traditionally focused on small solutes such as urea and creatinine, little attention has been paid to clearance of larger molecular weight uremic toxins, the so-called "middle molecules" and protein-bound uremic toxins which may have important pathophysiological impacts on mortality and morbidity. It is important to note the current PD prescription approach is moving away from just delivering "adequate dialysis" to a more "goal-directed" approach where the PD regimen is tailored to the individual patient's lifestyle and health goals [19]. In this approach, small solute clearance target values only form a part of the assessment of the quality of dialysis delivered, and the emphasis is on the assessment and management of more meaningful measures such as patient-reported outcomes, blood pressure control, quality of life, nutrition, and cardiovascular risk factors.

Investigations of the impact of PD dose have largely focused on patient survival, but have also looked at several other outcomes, including technique survival, hospitalization, nutritional status, and quality of life. In this chapter, we will focus on the existing evidence with respect to the impact of peritoneal solute clearance and residual kidney function (RKF) on patient survival, as well as evidence for the targets that are currently in use. We will also discuss strategies to optimize peritoneal solute clearance and preserve RKF, providing evidence when available. (Refer to Table 45.1).

Definitions

It has been conventional for PD adequacy to be measured in terms of small solute clearance. The solutes usually measured for theses indices are urea and creatinine. To compare clearance values among patients, these values are normalized to a function of patient size. For urea, the metric is typically the volume of urea distribution (V), which equates to total body water, and creatinine is typically is normalized to 1.73 m^2 body surface area (BSA). V is usually estimated from published formulas such as the Watson formula and BSA estimated using the Dubois formula [20, 21]. The fractional clearance of urea is expressed as Kt/V_{urea}, which is the clearance of urea (K) per time unit (t) in relation to its volume of distribution or total body water (V), and the fractional clearance of creatinine is known as creatinine clearance (CrCl). In both cases, the clearance includes both peritoneal and kidney clearances of these solutes. The dialytic component is calculated by measuring the urea and creatinine content of a 24-hour collection of dialysate effluent. These values are then divided by the serum urea and creatinine levels, respectively, to give the

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Table 45.1 Dialysis adequacy targets and preservation of RKF in PD patients.

Treatment	Recommendation	Certainty of evidence	Strength of recommendation
Total (peritoneal + kidney) Kt/V_{urea}	We suggest that achieving a total weekly Kt/V_{urea} in the range between 1.7–2.0 and >2.0 probably makes little or no difference to patient survival (moderate certainty evidence) A Kt/V_{urea} of <1.7 may lead to an increased risk of patient death (low certainty evidence)	Moderate (Kt/V 1.7–2.13) Low ($Kt/V < 1.7$)	Weak [1–5]
RAS inhibitors	We suggest that RAS blockers can be used to reduce RKF decline in PD patients	Moderate	Weak [6]
PD modality	We suggest that PD modality may make little or no difference to RKF decline	Low	Weak [7]
Use of diuretics	We suggest that diuretics may make little or no difference to RKF in PD patients, but may increase urine output	Low	Weak [8]
Use of aminoglycosides	We suggest that it is uncertain whether or not aminoglycosides hasten RKF decline in PD patients	Very low	Weak [9–13]
Dietary protein restriction	We suggest that dietary protein restriction coupled with keto-acid supplementation may help reduce RKF decline in PD patients	Low	Weak [14]
Neutral pH low GDP solution	Refer to Chapter 47, the certainty of evidence is high and the strength of recommendation is strong.	Refer to Chapter 47	Refer to Chapter 47

GRADE assessment of the certainty of the evidence [15]: High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different* is low. Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different* is moderate. Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different* is high. Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different* is very high. *Substantially different = a large enough difference that it might affect decision-making.
PD, peritoneal dialysis; RAS, renin-angiotensin system; RKF, residual kidney function.

daily urea and creatinine clearance. The kidney component of urea and creatinine clearance is calculated in the same manner with a 24-hour urine collection, except that, in the case of creatinine clearance, an average of residual kidney urea and creatinine clearance is typically used. This is because creatinine clearance substantially overestimates the true glomerular filtration rate as creatinine is not only filtered but also secreted into the tubules. Both the Kt/V and CCr are expressed as weekly values and therefore the total daily values are multiplied by 7.

Epidemiology

According to the International Society of Nephrology Global Kidney Health Atlas 2019, only 58% of countries where PD is available measure small solute clearance (Kt/V_{urea}, CCr) [22]. Measurement and reporting of small solute clearance are closely correlated with national incomes. Nearly all high-income countries (85%) measure and report small solute clearance, compared to 45% of upper-middle, 17% of lower-middle, and none of the low-income countries. Importantly, countries in which there is no or limited ability to provide an adequate PD dose (defined as three to four exchanges per day or equivalent cycles on automated PD) were least likely to monitor and report small solute clearance.

The average total weekly urea Kt/V achieved in most countries was >2, except in Canada and Japan [23]. Average peritoneal Kt/V was highest in Thailand (1.73 in continuous ambulatory peritoneal dialysis [CAPD] patients) and lowest in Japan (1.09 and 1.16 on automated PD [APD] and CAPD patients, respectively). The correlation between achieved total Kt/V and daily number of PD exchanges and volume of dialysate is unclear. There is a large variation among countries in the number of exchanges used. No patients in Thailand compared to 40% of patients in Japan on APD use fewer than three exchanges. In the United States, clinics may be financially impacted by a failure of a proportion of PD patients at a clinic to achieve a total $Kt/V > 1.7$. It is tempting to surmise that the concern about reaching a Kt/V target may explain our observation that the

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United States has the lowest percentage of patients with $Kt/V < 1.7$ and the highest percentage with $Kt/V > 2$ among countries participating in the Peritoneal Dialysis Outcomes and Practice Patterns Study (PDOPPS) [23].

Pathophysiology of Solute Transport in Peritoneal Dialysis

The peritoneum is a serous semipermeable membrane composed of a thin layer of connective tissue covered by a mesothelial cell monolayer. It covers most of the abdominal wall and intraabdominal organs. The mesothelial cells at the peritoneal cavity side have abundant cytoplasmic extensions (microvilli), which have anionic fixed charges and play a role in the transmembrane transfer of small charged molecules as well as plasma proteins [24]. The mesothelial microvilli increase the effective peritoneal surface up to 40 m^2 although the surface area of the human adult peritoneum is only about 1.6–2.0 m^2 [25].

Solute transport occurs through both diffusion and convection. Diffusion involves solute movement across a semipermeable membrane due to the presence of a concentration gradient. Convection occurs when solutes move along with water during ultrafiltration by the process of solute drag. The two-pore theory proposed the presence of abundant small pores, 40–50 Å, and few larger pores, up to 150 Å, in the peritoneal membrane capillary endothelial wall through which solute and fluid transfer occur [26]. Subsequently the finding of transcellular (endothelial cells) ultra-small pores (aquaporin-1 channels, 3–5 Å) led to the proposal of a three-pore model, in which around 50% of the transcapillary ultrafiltration occurs through aquaporin-1 channels and the remainder mostly through small pores [27, 28].

The different factors influencing solute transport include solute concentration gradient across the peritoneal membrane, peritoneal membrane characteristics such as surface area available for transport (determined by the number of capillaries available and the area of peritoneal membrane in contact with the dialysate), water flux, solute reflection coefficient of the membrane and importantly the intrinsic permeability of the peritoneal membrane. Transport of low-molecular-weight (LMW) and medium-molecular-weight (MMW) solutes depends mostly on their size and the surface area available for transport and to a lesser degree on changes in the permeability of the peritoneum [29]. Transport of larger molecules is size-selective, therefore it depends on several variables, including effective membrane surface area, permeability of the membrane itself, and, importantly, the molecular size of the solute.

Assessing Peritoneal Transfer Rate

The peritoneal equilibration test (PET) is the most widely used test to characterize the rate of solute and water transfer in patients undergoing PD. Briefly, the overnight dialysate is drained and 2 l of 2.27% glucose (2.5% dextrose) dialysis fluid is infused and dialysate samples are taken after infusion and then after 2 and 4 hours, at which time the dialysate is drained and the volume recorded. A blood sample is drawn at 2 hours dwell time. Usually, the dialysate drainage volume (used as a measure of ultrafiltration capacity [UFC]) and D/P (dialysate/plasma ratio) for creatinine are compared with standard values [30].

Large population-based studies suggest that, on average, the concentration of creatinine in the dialysate at 4 hours is about two-thirds that in the blood (or 4-hour D/P creatinine is 0.67). It is conventional to assign patients a "transport" type based on the results of the PET as being low, low-average, high-average, or high transporters [30]. Individuals assigned as having an average transport are the ones that are within one standard deviation of the mean, and the ones with low or high transport are more than one standard deviation below or above the mean, respectively. The 4-hour D/P creatinine ratios for low, low-average, high-average, or high transporters are <0.5, 0.50–0.65, 0.65–0.81, and >0.81, respectively.

Assessment of Impact of Small Solute Clearance on Patient Survival

Understanding of the impact of small solute clearance on patient survival in PD has evolved over time. Early studies suggested a beneficial effect of small solute clearance, as assessed by Kt/V_{urea} and CrCl, on survival. The largest of these early studies was the Canada-USA (CANUSA) study, which evaluated the association between adequacy of PD and patient survival among 680 incident CAPD patients over 2 years [31]. In this study, total (kidney and peritoneal) small solute clearance was found to be an independent predictor of patient survival. Based on a fitted model, there was a 5% decrement in expected patient survival for every 0.1 decrease in total weekly Kt/V_{urea} for values between 1.5 and 2.3, and a 7% decrement in expected survival for every 5 l/week/1.73 m^2 decrease in CrCl. The assumption was that peritoneal and kidney contributions to small solute clearance were equivalent, and therefore additive. However, a subsequent re-analysis of the CANUSA data, focusing on the relative contributions of kidney and peritoneal clearances, provided new important insights into the impact of RKF on survival [32]. For each

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5 l/week/1.73 m^2 increase in kidney CrCl, there was a 12% decrease in the relative risk (RR) of death. Furthermore, each 250 ml increment in urine volume was associated with a 36% decrease in the RR of death. Neither peritoneal CrCl nor peritoneal ultrafiltration was associated with patient survival.

In 2002, the ADEMEX trial which was done to assess the effect of small solute clearance on survival was published. It remains the largest randomized controlled study published in the PD literature [1]. In this study, 965 incident and prevalent PD patients were randomized to a standard CAPD regimen of 2 l exchanges four times daily or a modified dialysis prescription to achieve a peritoneal CrCl of >60 l/week/1.73 m^2. To achieve this, individual dwell volumes were increased, followed by the addition of a fifth dwell if the target was not reached by 2 months. Patients were followed for a minimum of 2 years, with a primary endpoint of death. The mean age of patients enrolled was approximately 47 years, with an incidence of pre-existing ischemic heart disease that was low in both groups (<5%) and not different between the two. While the intervention group had significantly higher peritoneal Kt/V_{urea} than the control group (2.13 vs. 1.62) and peritoneal CrCl (57 vs. 46 l/week/1.73 m^2) than the control group, there was no difference in patient survival (69.3% vs. 68.3% at 2 years, RR 1.00 95% confidence interval [CI] 0.80–1.24). The major cause of death in both groups was ischemic heart disease. In the control group, a higher death rate due to congestive heart failure and a combination of uremia/hyperkalemia/acidosis was reported. It is worth pointing out that hyperkalemia and acidosis are complications that rarely occur in PD patients, and it is especially rare to be severe enough to cause death. Since a composite endpoint of death due to uremia/hyperkalemia/acidosis was used, it is possible that uremia accounted for the majority of the difference between the groups. It is also reported that more patients in the control group withdrew from the study because of uremia. Unfortunately, uremia was not specifically defined, and since the study was not blinded, this may have introduced a significant bias. Knowing which patients were receiving a lower dialysis dose may have led physicians to attribute nonspecific symptoms or death in the control group to uremia. With regard to the higher mortality related to congestive heart failure in the control group, this is not necessarily attributable to underdialysis. Rather, it can instead be plausibly explained by a difference in ultrafiltration attributable to the use of an additional exchange in 22% of patients in the intervention group. In fact, the intervention group had approximately 100 cc/day more ultrafiltration on average than the control group. In contrast to peritoneal clearance in this study, kidney Kt/V_{urea} and kidney CrCl did emerge as predictors of improved outcome, with a RR of 0.89 per 10 l/week/1.73 m^2 increase in CrCl and 0.94 per 0.1 increase in Kt/V_{urea}.

Another randomized controlled trial by Lo et al. confirmed the lack of survival benefit with increased peritoneal clearance [2]. In this study, 320 incident CAPD patients were randomly assigned to one of three groups, Kt/V_{urea} 1.5–1.7, 1.7–2.0 or >2.0, and followed over 2 years. Patients with an initial kidney Kt/V_{urea} of greater than 1.0 were excluded. Kidney Kt/V_{urea} in the study patients was not significantly different between the groups, so that the difference in Kt/V_{urea} was accounted for by differences in peritoneal clearance. Overall, 2-year patient survival was 84.9%. After adjustment for age and diabetes, total Kt/V_{urea} did not affect survival in patients with $Kt/V_{urea} > 2.0$ vs. 1.7–2.0, although there was a trend toward better survival in patients with Kt/V_{urea} 1.7–2.0 vs. 1.5–1.7 ($P = 0.054$).

Given the overarching effect of RKF on survival, dose of PD may be more important in those who have lost their RKF. Two prospective studies in anuric PD patients using Kt/V_{urea} and CrCl have shown a statistically significant association between peritoneal clearance and better survival [33, 34]. The first study to show a positive association between peritoneal clearance and survival was performed by Szeto et al. and involved 140 anuric CAPD patients followed for 22 months [33]. In this group, it was estimated that there was a 6% decrease in the RR of death with an increase in Kt/V_{urea} of 0.1/week and a 12% decrease in the RR of death for each 5 l/week/1.73 m^2 increase in peritoneal CrCl. Jansen et al. followed a cohort of 130 anuric CAPD patients over 2 years [34]. While peritoneal Kt/V_{urea} and CrCl were not associated with survival when analyzed as continuous variables, when the results were analyzed dichotomously, a weekly Kt/V_{urea} of <1.5 compared to >1.5 (RR 3.28, 95% CI 1.25 to 8.60, $P = 0.02$) and a weekly CrCl <40 l/1.73 m^2 compared to >40 l/1.73 m^2 (RR 3.26, 95% CI 1.24 to 8.55, $P = 0.02$) were associated with an increased RR of death. Fried et al., in a retrospective study of 1432 anuric PD patients, found that when adjusted for age, sex, race, diabetes, and serum albumin level Kt/V_{urea} of <1.7 was associated with significantly higher risk of mortality and hospitalization [4]. Adjusted CrCl on the other hand did not predict mortality.

The findings from various studies on the effect of small solute clearances in all PD patients and in anuric PD patients are summarized in Tables 45.2 and 45.3, respectively.

Overall, there is now evidence from two randomized trials and several supporting observational studies to suggest that while the total clearance is important, improved patient survival appears to be more strongly associated with kidney clearance and not peritoneal clearance.

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Table 45.2 Summary of studies assessing effect of small solute clearance on mortality in PD patients.

Study	Study design	No. of patients	Follow-up (months)	Predictor	Outcome (mortality) Measure-RR, OR or HR (95% CI)		
					Renal	Peritoneal	Total
Paniagua 2002 [1]	RCT	965	22	$Kt/V \uparrow 0.1$ U/week	RR 0.94 (NA) ($P = 0.005$)	RR 1.00 (CI-NA)	
Lo 2003 [2]	RCT	320	24	$Kt/V \uparrow 0.1$ U/week			RR0.94 (0.87–1.02)
Lo 2001 [45]	Prospective cohort	937	24	$Kt/V \uparrow 0.1$ U/week			Kt/V-RR 0.95 (0.90–1.01) CrCl-RR 0.99 (0.98–1.00)
				pCrCl ↑ 1 l/week/1.73 m^2			
Rocco 2000 [38]	Prospective cohort	873	7	$Kt/V \uparrow 0.1$ U/week	OR 0.88 (0.81–0.96)[a]	OR 1.00 (0.90–1.10)	OR = 0.6 (0.40–1.10)
Bargman 2001 [32]	Prospective cohort	601	24	rGFR ↑ 5 l/week/1.73 m^2	RR 0.88 (0.83–0.94)[a]		
				pCrCl ↑ 5 l/week/1.73 m^2		RR 1.00 (0.90–1.10)	
Termoshuizen 2003 [47]	Prospective cohort	413	36	rGFR ↑ 1 ml/min/1.73 m^2	RR 0.88(0.79–0.99)[a]		
				pCrCl ↑ 1 ml/min/1.73 m^2		RR = 0.91 (0.71–1.17)	
Szeto 2004 [39]	Prospective cohort	270	35	rGFR ↑ 1 ml/min/1.73 m^2	RR 0.80 (0.73–0.88)[a]		
				$Kt/V \uparrow 0.1$ U/week		RR 0.94 (0.89–0.99)[a]	
Szeto 2000 [40]	Prospective cohort	270	22	rGFR ↑ 1 ml/min/1.73 m^2	RR 0.48 (0.02–0.93)[a]		
				$Kt/V \uparrow 0.1$ U/week			RR 0.96 (0.93–0.99)[a]
Wang 2004 [41]	Prospective cohort	231	30	RKF vs. no RKF	No RKF:↑ mortality (RR and 95% CI- NA)[a]		
Davies 1998 [49]	Prospective cohort	210	6	$Kt/V \uparrow$ per unit weekly			RR 0.17(95% CI-NA)[a]
Szeto 2001 [33]	Prospective cohort	140	22	$Kt/V \uparrow 0.1$ U/week CrCl ↑ 5 l/week/1.73 m^2		RR 0.94 (0.92–0.99) [a] RR 0.88 (0.76–0.99) [a]	
Jager 1999 [48]	Prospective cohort	118	25	$Kt/V \uparrow 0.1$ U/week	RR 0.96 (0.88–1.05)	RR 0.95 (0.84–1.08)	RR 0.93 (0.85–1.02)
				CrCl ↑ 5 l/week/1.73 m^2	RR 0.97 (0.91–1.03)	RR 0.96 (0.81–1.13)	RR 0.96 (0.89–1.03)
					Renal	Peritoneal	Total
Chung 2003 [46]	Prospective cohort	82	14	rGFR ↑ 1 ml/min/1.73 m^2	RR = 0.79 (0.55–1.08)		
				$Kt/V \uparrow 0.1$ U/week			RR 1.09 (0.96–1.24)
Maiorca 1995 [35]	Prospective cohort	68	36	Kt/V/week ≥1.96 vs. <1.96			RR 0.10 (0.01–0.72)*a*
Diaz-Buxo 1999 [37]	Retrospective	1603	12	CrCl ↑ 10 l/week/1.73 m^2	OR 0.88 (95% CI-NA)*a*	OR 1.01 (95% CI-NA)	OR 0.89 (95% CI-NA)

(*Continued*)

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Table 45.2 (Continued)

Study	Study design	No. of patients	Follow-up (months)	Predictor	Outcome (mortality) Measure-RR, OR or HR (95% CI)		
					Renal	Peritoneal	Total
Rocco 2002 [42]	Retrospective	1219	12	*Kt*/*V*/week 0.00–0.14 vs >0.77	HR = 2.13 (1.24–3.68)*a*		
				Kt/*V*/week 0.15–0.40 vs. >0.77	HR = 1.67 (0.87–3.20)		
				Kt/*V*/week 0.41–0.77 vs. >0.77	HR = 1.35 (0.70–2.62)		
Park 2001 [50]	Retrospective	212	36–84	*Kt*/*V*/week >2.1 vs. <2.1			*Kt*/*V* not found to be predictor of mortality RR and CI not available from paper
Genestier 1995 [36]	Retrospective	201	24	*Kt*/*V*/week <1.7 vs. >1.7			RR 1.69 (0.89–3.19)*a*
				CrCl <50 l/week vs. >50 l/week			RR 4.88 (2.04–11.71)*a*
Ates 2001 [44]	Retrospective	125	31	rGFR ↑ 1 ml/min/1.73 m^2	RR = 0.53 (0.31–0.92)*a*		
Bhaskaran 2000 [51]	Retrospective	122	27	p*Kt*/*V*/week >1.85 vs. <1.85		RR = 0.54 (0.26–1.13)	
Chung 2003 [43]	Retrospective	117	20	RKF 1 ml/min	RR = 0.79 (0.55–1.08)		
				Kt/*V* ↑ 0.1 U/week			RR 1.09 (0.96–1.24)
Rumpsfeld 2009 [3]	Retrospective	2434	3267 patient-years	*Kt*/*V* < 1.45 vs. 1.70–2.00			HR 1.87(1.24–2.84)*a*

CI, confidence interval; CrCl, creatine clearance; HR, hazard ratio; NA, not available from published data; OR, odds ratio; PD, peritoneal dialysis; rGFR, residual glomerular filtration rate; RCT, randomized controlled trial, RKF, R, residual kidney function; RR, relative risk.
[a] $P < 0.05$.

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Table 45.3 Summary of studies assessing effect of small solute clearance on mortality in anuric PD patients.

Study	Study design	No. of patients	Follow-up	Predictor	Outcome RR (95% CI)
Paniagua 2002 [1]	RCT (subgroup analysis)	527	22	$Kt/V \uparrow 0.1$ U/week	Not significantly different between comparator groups according to authors RR, 95% CI not mentioned in study report
Szeto 2001 [33]	Prospective	140	22	$Kt/V \uparrow 0.1$ U/week	RR 0.94 (0.92–0.99)[a]
Jansen 2005 [34]	Prospective	130	24	Kt/V/week < 1.5	RR 3.28 (1.25–8.60)
				CrCl <40 l/week/1.73 m^2	RR 3.26 1.24–8.55[a]
Brown 2003 [52]	Prospective	177	24	Time-averaged total CrCl	RR 1.01 95% CI-NA
Bhaskaran 2000 [51]	Retrospective	122	27	pKt/V/week >1.85 vs. <1.85	RR 0.54 (0.26–1.13)
Fried 2008 [4]	Retrospective	1432	Median 290 days	$Kt/V < 1.5$	Mortality rate/100 person-years −23.7 (−40.0 to −2.9)[a]
Lo 2005 [5]	Retrospective	150	50	$Kt/V < 1.67$	RR 1.98 (1.18–3.33)[a]

CI, confidence interval; CrCl, creatine clearance; HR, hazard ratio; NA, not available from published data; PD, peritoneal dialysis; RCT, randomized controlled trial; RR, relative risk.
[a] $P < 0.05$.

The basis for the survival advantage associated with RKF is unclear, with several possible contributors. First, the presence of residual urine output facilitates volume management, which may have a favorable effect on blood pressure control and subsequent left ventricular geometry [53, 54]. Both hypertension and left ventricular hypertrophy are associated with loss of RKF and are known to be independent predictors of mortality in PD patients [55]. Second, RKF allows for clearance not only of small solutes but also middle molecules [56–58]. The latter are not as easily removed across the peritoneal membrane due to the time dependence of their diffusion and the limited permeability of the peritoneal membrane. Finally, patients with preserved RKF may represent a population who are intrinsically healthier and thus more likely to survive.

Summaries of findings with regards to the effect of targeting weekly CrCl of >60 l/week and different Kt/V targets are given in Tables 45.4–45.6.

Recommended Targets and Monitoring of PD Adequacy

Based on moderate certainty evidence, increasing Kt/V beyond 1.7 does not appear to have an impact on patient survival. Weekly Kt/V levels below 1.7 may be associated with an increased risk of death (low certainty evidence), although a minimum total weekly Kt/V target has not been definitively established.

Adequacy targets and frequency of monitoring as recommended by the various kidney societies are summarized in Table 45.7. The current International Society for Peritoneal Dialysis (ISPD) guidelines for PD prescription recommend measurement of Kt/V_{urea} or CrCl to provide a quantitative measure of amount of dialysis delivered, but do not recommend achieving a minimum target of Kt/V_{urea} given the poor quality of evidence linking achieving a Kt/V_{urea} of >1.7 to survival. According to this guideline, PD prescription should be tailored to the individual patient's lifestyle and healthcare goals based on multidimensional assessment of several factors, such as quality of life, patient-reported outcomes, nutrition, etc., to maintain quality of life, minimize symptoms and treatment burden, and ensure high-quality care [59]. Given the inaccuracies in the measurement of Kt/V_{urea}, the guideline recommends using a range of acceptable Kt/V_{urea} for the individual patient rather than a single cut-off value. All of the other renal society guidelines in general recommend a total (kidney + peritoneal) weekly Kt/V_{urea} of 1.7 [60–63]. The European Best Practice Guideline (EBPG) states a weekly Kt/V_{urea} target of 1.7 only for anuric PD patients and does not make any specific recommendations for those with RKF [63]. The Renal Association (UK) recommends a total (kidney + peritoneal) weekly Kt/V_{urea} of 1.7 or CrCl of 50 l/week/1.73 m [61]. The ISPD recommends an additional target of 45 l/week/1.73 m^2 CrCl for APD patients [59]. The EBPG recommends the same CrCl target (45 l/week/1.73 m^2) for APD patients who are on short frequent exchanges with slow transport status [63]. It is important to point out that while these minimum targets do not differentiate between kidney and peritoneal contributions, it is clear that kidney and peritoneal clearance are not simply

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Table 45.4 Summary of findings: PD prescription adjusted to achieve peritoneal CrCl of 60 l/week (actual achieved total Kt/V_{urea} 2.27) versus standardized PD prescription of four 2 l exchanges/day (actual achieved total Kt/V_{urea} 1.8).

	PD prescription adjusted to achieve peritoneal CrCl of 60 l/week (actual achieved total Kt/V_{urea} 2.27) versus standardized PD prescription of four 2 l exchanges/day (actual achieved total Kt/V_{urea} 1.8)				
Outcomes	**No of participants (studies)**	**Absolute effect (95% CI)**	**Relative effect (95% CI)**	**Quality of the evidence (GRADE)**	**Conclusion**
All-cause mortality	965 (one RCT)	Seven more per 1000 (from 48 fewer to 72 more)	RR 1.02 (0.85 to 1.22)	⊕⊕⊕⊕ High	Target CrCl of 60 l/week in PD patients will have little or no effect on all-cause mortality

CI, confidence interval; CrCl, creatine clearance; PD, peritoneal dialysis; RCT, randomized controlled trial; RR, relative risk.

Table 45.5 Summary of findings: total Kt/V_{urea} 1.7 to 2.0 versus total Kt/V_{urea} 1.5–1.7.

	Total Kt/V_{urea} 1.7 to 2.0 versus total Kt/V_{urea} 1.5 to 1.7				
Outcomes	**No of participants (studies)**	**Absolute effect (95% CI)**	**Relative effect (95% CI)**	**Quality of the evidence (GRADE)**	**Conclusion**
All-cause mortality	208 (one RCT)	39 more per 1000 (from 55 fewer to 198 more)	RR 1.20 (0.71–2.03)	⊕⊕⊖⊖ Low	Achieving a total Kt/V_{urea} of 1.7 to 2.0 in PD patients may make little or no difference to all-cause mortality

CI, confidence interval; PD, peritoneal dialysis; RCT, randomized controlled trial; RR, relative risk.

Table 45.6 Summary of findings: total $Kt/V_{urea} > 2.0$ versus total Kt/V_{urea} 1.7–2.0.

	Total $Kt/V_{urea} > 2.0$ versus total Kt/V_{urea} 1.7 to 2.0				
Outcomes	**No of Participants (studies)**	**Absolute effect (95% CI)**	**Relative effect (95% CI)**	**Quality of the evidence (GRADE)**	**Conclusion**
All-cause mortality	216 (one RCT)	Two more per 1000 (from 88 fewer to 147 more)	RR 1.01 (0.62–1.64)	⊕⊕⊖⊖ Low	Achieving a total $Kt/V_{urea} > 2.0$ in PD patients may make little or no difference to all-cause mortality

CI, confidence interval; PD, peritoneal dialysis; RCT, randomized controlled trial; RR, relative risk.

additive, in that any small solute clearance provided by RKF is accompanied by improved clearance of middle molecules and better salt and water control.

In keeping with the current ISPD guideline on PD prescription and the limitations of current techniques to assess clearance, a patient's clinical status must always be considered when trying to determine the adequacy of dialysis. The outcome of interest in the studies discussed has principally been survival. There are no rigorous studies prospectively examining dose of PD and health outcomes other than death. Therefore, the guidelines all suggest that the dose be increased as a trial in the patient not doing well for reasons not explained by comorbidity, regardless of their current prescription.

To ensure a total delivered Kt/V_{urea} that is commensurate with optimal clinical wellbeing of the patient using a multidimensional assessment, solute clearances can be followed with the use of 24-hour collections of dialysate and urine. While data on frequency of measurements are sparse, we would recommend the following schedule. If small solute clearance is going to be monitored, the first measurement of peritoneal and kidney Kt/V_{urea} should be

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Table 45.7 Summary of guidelines on small solute clearance targets and frequency of PD adequacy testing.

Renal society	Small solute clearance targets	Frequency of measurement
International Society of Peritoneal Dialysis (ISPD) [59]	Small solute clearance should be routinely measured using Kt/V_{urea} or creatinine clearance to provide a quantitative measure of the amount of dialysis delivered It does not recommend achieving a minimum target of Kt/V_{urea} given the poor quality of evidence linking achieving a Kt/V_{urea} of >1.7 to survival In setting a Kt/V_{urea} target for the individual patient, defining an acceptable range that recognizes the uncertainty of the measurement, rather than applying a single cut-off value is more appropriate	Not stated explicitly in the guideline other than it should be routinely measured
Kidney Diseases Outcomes Quality Initiative (KDOQI) [60]	For patients with RKF (urine volume > 100 ml/day), total weekly (renal + peritoneal) Kt/V_{urea} should be at least 1.7/week For patients without RKF (urine volume < 100 ml/day) peritoneal Kt/V should be at least 1.7	If patients have RKF, total clearance should be measured within 4 months and at least once every 4 months thereafter If patients do not have RKF, peritoneal Kt/V should be measured within the first month and at least every 4 months thereafter
Renal Association (UK) [61]	Total weekly (renal + peritoneal) Kt/V_{urea} should be 1.7/week or a creatinine clearance of 50 l/week/1.73 m^2	Both residual urine and peritoneal dialysis components of small solute clearance should be measured at least 6-monthly or more frequently if dependent on residual kidney function
Canadian Society of Nephrology [62]	PD prescription to achieve a total weekly Kt/V_{urea} of at least 1.7	Residual renal urine volume and residual renal Kt/V (rKt/V) should be measured every 3–6 months in patients with a peritoneal Kt/V (pKt/V) of less than 1.7 weekly, especially if RKF is rapidly declining In all other PD patients, rKt/V and urinary volume should be measured together with pKt/V when clinically indicated A measurement of total Kt/V should be carried out 4–6 weeks after initiation of PD The measurement of total Kt/V should be repeated if there is an unexplained or unexpected change in the patient's clinical status or a problem with ultrafiltration
European Best Practice Guidelines [63]	Minimal weekly peritoneal Kt/V_{urea} of 1.7 for anuric patients In APD patients using short frequent exchanges and slow transporter status, an additional target of 45 l/week/1.73 m^2 for peritoneal creatinine clearance is recommended	None recommended

APD automated peritoneal dialysis, PD, peritoneal dialysis; RKF, residual kidney function.

performed approximately 1 month after initiation of PD. Subsequent monitoring of peritoneal clearance is controversial. While the K/DOQI guidelines recommend checking peritoneal clearance at least once every 4 months, the peritoneal Kt/V_{urea} is unlikely to change in patients with a stable PD prescription [60]. Therefore, an alternative approach would be to re-measure peritoneal clearance only if changes are made to the PD prescription or if there is deterioration in the patient's clinical status. In the event of an episode of peritonitis, peritoneal clearance measurements should not be made until at least 1 month after resolution of the peritonitis because the inflammation can affect the trans-peritoneal transport of solutes. If a patient has >100 cc/day of residual urine output and achieving a total weekly Kt/V_{urea} of at least 1.7 is dependent on the kidney contribution, a 24-hour urine collection to assess kidney Kt/V_{urea} and urine volume should be performed regularly to avoid missing a decline in RKF.

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Strategies for Optimizing Peritoneal Solute Clearance

The routine measurement of small solute clearance serves to screen patients for evidence of underdialysis. If a patient is not meeting the minimum recommended PD dose, the basis for this should be determined. Before assuming that a given PD prescription is inadequate, patient-related causes of failure, such as adherence, lack of understanding or sampling and collection errors, should be sought. If none of these potential causes is found, several strategies can be employed to optimize a patient's PD prescription to improve peritoneal solute clearance. Common interventions include increasing the dwell volumes, increasing the frequency of exchanges or increasing peritoneal ultrafiltration [64, 65]. While the focus of these interventions is often to increase peritoneal small solute clearance, the importance of middle molecule clearance must also be considered, especially in patients with little or no RKF.

Increasing dwell volumes is an effective means by which peritoneal small solute clearance can be increased in both CAPD and APD patients [66]. The increase in Kt/V_{urea} and CrCl is due to both an increased plasma-to-dialysate concentration gradient and an increased effective peritoneal surface area [67, 68]. While increasing dwell volumes is often effective, this strategy leads to increased intra-abdominal pressure, which may lead to back pain and a higher risk of abdominal wall leaks and hernias [69], although this has not been borne out in some other studies [70–72]. The lower intra-abdominal pressure in the supine position may make increasing dwell volumes easier during the overnight exchange in CAPD patients or during the night exchanges in APD patients [73]. An additional concern is that increasing exchange volumes may limit peritoneal ultrafiltration by increasing intra-abdominal pressure, but the greater persistence of the osmotic gradient is likely to offset this [74].

Another commonly used strategy is increasing the frequency of exchanges. In patients on CAPD, this may require increasing from three to four or from four to five exchanges daily. Potential disadvantages include the burden an additional manual exchange places on the patient, and a decrease in middle molecule clearance due to a greater proportion of time spent draining and filling with less time for dialysate to dwell in the peritoneal cavity. In patients on cycler-based therapy, we advise against the use of nocturnal intermittent PD (NIPD) unless a significant amount of RKF remains or other special mitigating circumstances exist. An excellent method of increasing clearance in patients on NIPD is to add a day dwell. Maximizing the time spent with dialysate in the peritoneal cavity, especially with the use of a long dwell, is an important strategy because this leads to improvement in clearance of both small and larger solutes. While increasing the frequency of night-time cycles can also augment peritoneal small solute clearance by maximizing the concentration gradient between blood and dialysate, there are some concerns with this strategy [75]. First, if the cycles become too short, especially with larger dwell volumes, clearance of both small and larger solutes will diminish owing to "lost time" draining and filling [76]. In addition, rapid cycling can lead to reduced net sodium removal due to sodium sieving [77]. For these reasons, we do not recommend routinely increasing frequency of cycles on APD to optimize peritoneal clearance.

Increasing peritoneal ultrafiltration is another method of increasing peritoneal clearance. Raising the gradient for diffusion with the use of hypertonic glucose or icodextrin is the primary means by which ultrafiltration can be increased, with the additional fluid removal leading to increased clearance via convective transport [78, 79]. However, use of long-term hypertonic glucose as a method to optimize peritoneal clearance is not generally recommended given the potential deleterious effects on the peritoneal membrane and increased glucose loading [80]. Icodextrin is a viable option for the long dwell in patients in whom poor ultrafiltration is an issue but is not generally recommended for the sole purpose of increasing clearance [81]. A systematic review of biocompatible PD fluids showed that icodextrin did not improve small solute clearance, as determined by peritoneal creatinine clearance (three studies, standard mean deviation 0.36, 95% CI −0.24 to 0.96, $P = 0.020$) [82].

Ultimately, the decision as to which strategy to use to optimize peritoneal solute clearance will depend on the individual patient. Factors to consider include peritoneal membrane characteristics, the potential impact of increasing intra-abdominal pressure, and the patient's abilities and preferences. In general, attention should be focused on maximizing the contact time of dialysate in the peritoneal cavity.

Strategies for Preserving Residual Kidney Function

Because of the impact of RKF on the outcome of patients on PD, its preservation should be considered important. Strategies to preserve RKF include use of medications that might slow the decline in RKF and avoidance of agents known to have deleterious effects. Because of the paucity of data, many of our current practices are extrapolated from patients with chronic kidney disease.

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Biocompatible Fluids

The effect of neutral pH, low-glucose degradation product (GDP) solutions on RKF has been looked at in numerous studies, with several showing a protective effect [82]. There is some debate as to whether this benefit is due to a direct protective effect or whether the finding is associative and related to the decrease in peritoneal ultrafiltration (UF) seen in many of the same studies [83]. For an extensive review of the studies on biocompatible solutions and RKF, refer to the chapter 47 on PD solutions.

RAS Blockade

Table 45.8 summarizes studies on the effect of renin angiotensin system (RAS) blockade in PD patients [11, 84–92]. While this strategy is known to be effective in both hypertensive and normotensive patients with many forms of chronic kidney disease, the data in patients on dialysis are not as robust. Overall, in moderate certainty evidence, angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) therapy administered for 12 months or more probably reduces the rate of RKF decline in patients receiving chronic PD. Summaries of findings with regards to the effect of RAS blockade on RKF are given in Tables 45.9–45.13.

Aminoglycosides

Aminoglycosides are frequently used to treat peritonitis in PD patients because of their effectiveness as bactericidal agents and the ease of intraperitoneal administration. They are, however, also nephrotoxic. Several prospective cohort studies and one randomized controlled trial have assessed the effect of aminoglycosides on RKF. These studies are summarized in Table 45.14.

In a randomized, controlled trial, Lui et al. compared the use of cefazolin and ceftazidime with cefazolin and netilmicin for the empiric treatment of peritonitis in 50 PD patients with RKF [9]. In both groups there was a significant decline in RKF at 2 weeks which returned to near baseline by 6 weeks, but there was no significant difference in RKF between the groups. While this represents the only randomized study of aminoglycosides and RKF, the follow-up period was short, and some of the patients in the aminoglycoside group were exposed to only a few days of netilmicin. The summary of findings from the data in this study is presented in Table 45.14.

Shemin et al. assessed the rate of decline of RKF in 72 PD patients followed for 4 years [10]. Patients who had peritonitis episodes treated with intraperitoneal or intravenous aminoglycosides had more rapid decline in kidney creatinine clearance and residual urine volume than either those who had never had a peritonitis episode or those who had peritonitis treated with other non-nephrotoxic antibiotics. In another study analyzing the risk factors associated with a faster rate of decline, use of aminoglycosides was found to be an independent predictor of a more rapid loss of RKF [11]. In contrast to the findings in the above studies, Baker et al., using a prospective cohort design with a historical control, did not find an accelerated decline in RKF with the use of aminoglycosides to treat peritonitis [12]. One large retrospective study looked at the slope of RKF decline in 2715 Australian patients and compared the slope of RKF decline in the 1075 patients who received at least one course of aminoglycoside for peritonitis compared to those who had not received any aminoglycosides [13]. The slopes of RKF decline were found to be the same in both groups, suggesting that treatment of peritonitis with aminoglycosides was not associated with an adverse impact on RKF in PD patients. In very low certainty evidence, it is uncertain whether aminoglycosides lead to faster RKF decline.

A summary of the findings with regards to the effect of aminoglycosides on RKF is given in Table 45.15.

Iodinated Radiocontrast Media

Two small, prospective studies have addressed this issue [93, 94]. Dittrich et al. assessed RKF (mean of 24-hour urine urea and CrCl) in 10 PD patients who were given iodinated radiocontrast media and compared them with eight control patients who did not receive radiocontrast media [92]. Patients who received radiocontrast media showed an initial decline in RKF reaching its lowest point by 6 days after contrast administration (3.78 ml/min/1.73 m^2, interquartile range [IQR] 2.56–6.77 vs. baseline 5.50 ml/min/1.73 m^2, IQR 2.91–8.10). However, after 30 days, there was no difference in either patient group compared to baseline values. In the study by Moranne et al. RKF (mean of 24-hour urine urea and CrCl) was compared between 36 PD patients who received iodinated radiocontrast media and 36 comparable patients who did not receive radiocontrast media [93]. RKF was measured prior to and 2 weeks after contrast media administration. In those who received contrast media, RKF values were not significantly different prior to and 2 weeks after contrast administration (mean 7.0 vs. 7.2 ml/min/1.73 m^2, $P = 0.12$). When compared to the control group, those who

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Table 45.8 Summary of studies assessing effect of RAS blockade on RKF in PD patients.

Study	Study Design	No. of patients	Follow-up time (moment)	Comparison	Outcome	Results: mean (SD) unless stated otherwise
Li 2003 [86]	RCT	60	12	ACEi vs. other anti-hypertensive	Slope of residual GFR decline ml/min/1.73 m^2	ACEi 2.07 (1.12) vs. control 3.00 (1.86)[a]
					Hazard of developing anuria at 12 mmol/min per 1.73 m^2 Rate of decline in residual GFR Rate of decline in residual GFR Rate of decline in residual GFR	HR for anuria 0.58 (95% CI 0.36–0.94)
Suzuki 2004 [87]	RCT	34	24	ARB vs. other antihypertensive	End of study residual GFR ml/min/1.73 m^2	ARB 4.3 (0.7) vs. control 2.8 (0.4)[a]
Zhong 2007 [89]	RCT	44	12	ARB vs. antihyptertensive other than ACEi or ARB	End of study residual GFR ml/min	ARB 1.68 (0.86) vs. control 1.04 (0.66)[a]
Wang 2005 [88]	RCT	32	28 ± 13	ARB vs. antihyptertensive other than ACEi or ARB	End of study residual GFR change ml/min	ARB 3.88 (2.55) vs. control 2.57 (2.88)
Phakdeekitcharoen 2004 [90]	RCT-crossover	29	8 weeks (4 weeks in each arm)	ACEi vs. ARB	Change in residual GFR ml/min/1.73 m^2	Mean values: −0.06 (ARB) vs. +0.24 (ACEi), P = NS SD-NA
Reyes-Martin 2012 [91]	RCT	60	12	ACEi vs. ARB	Slope of RKF decline ml/min/1.73 m^2	ARB 2.54 (0.47) vs. ACEi 2.36 (0.38)
Singhal 2000 [11]	Prospective	242	27	ACEi vs. no ACEi	Slope of GFR decline	ACEi −0.14 (+0.20) vs. control −0.16 (0.20)
Johnson 2003 [85]	Prospective	146	21	ACEi vs. no ACEi	Time to anuria	HR = 0.81 (95% CI 0.52 to 1.27)
Moist 2000 [84]	Retrospective	1032	18	ACEi vs. no ACEi	Odds for developing anuria (urine volume <200 ml/day)	OR = 0.70 (95% CI-NA) (P = 0.02)
Kolesnyk 2011 [92]	Retrospective	452	36	ACEi/ARB vs. no ACEi/ARB	Slope of decline of residual GFR ml/min/1.73 m^2	Authors report rate of decline in residual GFR was similar in both groups P = 0.23 after adjustment for confounding factors No other related numerical data supplied in study report

ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CI, confidence interval; GFR, glomerular filtration rate; HR, hazard ratio; NA, not available from study report; NS, not significant; OR, odds ratio; PD, peritoneal dialysis; RAS, renin angiotensin system; RCT, randomized controlled trial; RKF, residual kidney function; SD, standard deviation.
[a] $P < 0.05$.

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Table 45.9 Summary of findings: ARB use for 12–24 months versus non-RAS blockade antihypertensive treatment.

ARBs versus non-RAS blockade antihypertensives					
Outcomes	**No of participants (studies)**	**Assumed risk**	**Corresponding risk**	**Quality of the evidence (GRADE)**	**Conclusion**
Residual kidney function ml/min/1.73 m^2	110 (three RCTs)	Mean RKF in control (non-RAS blockade antihypertensives) group were from 1.04 to 2.80	Mean RKF in ARB group was 1.11 higher (0.38 higher to 1.83 higher)	⊕⊕⊕⊖ Moderate	Use of ARBs in PD patients may preserve RKF in PD patients

ARB, angiotensin receptor blocker; PD, peritoneal dialysis; RAS, renin angiotensin system; RCT, randomized controlled trial; RKF, residual kidney function.

Table 45.10 Summary of findings: ACEi use for 12 months versus non-RAS blockade antihypertensive treatment- effect on decline of RKF.

ACEi versus non-RAS blockade antihypertensives for 12 months					
Outcomes	**No. of participants (studies)**	**Assumed risk**	**Corresponding risk**	**Quality of the evidence (GRADE)**	**Conclusion**
Decline in residual GFR ml/min/1.73 m^2	53 (one RCT)	Mean value of decline in the control group was 3	Mean decline in ARB group was 0.93 lower (1.75 lower to 0.11 lower)	⊕⊕⊕⊖ Moderate	Use of ACEi may slow decline in RKF in PD patients

ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; GFR, glomerular filtration rate; PD, peritoneal dialysis; RAS, renin angiotensin system; RCT, randomized controlled trial; RKF, residual kidney function.

Table 45.11 Summary of findings: ACEi use for 12 months versus non-RAS blockade antihypertensive treatment- effect on risk of anuria.

ACEi versus non-RAS blockade antihypertensives for 12 months					
Outcomes	**No. of participants (studies)**	**Absolute effect (95% CI)**	**Relative effect (95% CI)**	**Quality of the evidence (GRADE)**	**Conclusion**
Anuria	60 (one RCT)	264 fewer per 1000 (from 7 fewer to 432 fewer)	RR 0.64 (0.41 to 0.99)	⊕⊕⊕⊖ moderate	Use of ACEi may reduce the risk of anuria over 12 months

ACEi, angiotensin converting enzyme; CI, confidence interval; RAS, renin angiotensin system; RCT, randomized controlled trial; RR, relative risk.

Table 45.12 Summary of findings: ARB versus ACEi use for 12 months for preservation of RKF.

ARB versus ACEi use for 12 months					
Outcomes	**No of participants (studies)**	**Assumed risk**	**Corresponding risk**	**Quality of the evidence (GRADE)**	**Conclusion**
Residual kidney function ml/min/1.73 m^2	60 (one RCT)	Mean RKF in control (ACEi) group was 2.36	Mean RKF in ARB group was 0.18 higher (0.03 lower to 0.39 higher)	⊕⊕⊕⊖ Moderate	There may be little or no difference between ARBs and ACEi with respect to preserving RKF in PD patients
Urine volume (ml/day)	60 (one RCT)	Mean daily urine volume in control (ACEi) group was 653	Mean daily urine volume in ARB group was 145 higher (8.35 lower to 298.35 higher)	⊕⊕⊕⊖ Moderate	There may be little or no difference between ARBs and ACEi with respect to preserving urine volume in PD patients

ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; PD, peritoneal dialysis; RCT, randomized controlled trial; RKF, residual kidney function.

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Table 45.13 Summary of findings: ARB versus ACEi use for 12 months, effect on risk of anuria.

ARB versus ACEi use for 12 months					
Outcomes	**No. of participants (studies)**	**Absolute effect (95% CI)**	**Relative effect (95% CI)**	**Quality of the evidence (GRADE)**	**Conclusion**
Anuria	60 (one RCT)	33 fewer per 1000 (from fewer to 432 fewer)	RR 1.09 (0.57 to 2.07)	⊕⊕⊕⊖ moderate	There may be little or no difference between ARBs and ACEi with respect to reducing risk of anuria

ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CI, confidence interval; RCT, randomized controlled trial; RR, relative risk.

received contrast media did not have a significant difference in variation in RKF over the 2-week study period (mean 0.1 vs. 0.1 ml/min/1.73 m^2, $P = 0.9$). Nevertheless, given the small numbers of patients in these dialysis studies and the clear data in patients with chronic kidney disease (CKD), it would be prudent to avoid using radiocontrast media if other acceptable alternatives exist. If use of radiocontrast dye is required, volume contraction should be avoided, and the smallest volume of the least toxic dye should be used.

Dietary Intervention

One small Chinese trial randomized 20 stable PD patients each to diets containing 0.6–0.8 g of protein/kg ideal body weight/day supplemented with 0.12 g/kg ideal body weight/day keto acids (group sLP), 0.6–0.8 g of protein/kg ideal body weight/day (group LP), or 1.0–1.2 g of protein/kg ideal body weight/day (group HP) [14]. All patients had >800 ml/day urine output or estimated glomerular filtration rate (eGFR) >2 ml/min/1.73 m^2. Seven patients dropped out during the study. Follow-up period was 12 months. At the end of study period, a significant decline in RKF was noted in the HP (4.25 ± 2.34 to 2.55 ± 2.29 ml/min/1.73 m^2, $P < 0.05$) and LP groups (4.02 ± 2.49 to 2.29 ± 1.72 ml/min/1.73 m^2, $P < 0.05$) but no such decline was noted in the sLP group (3.84 ± 2.17 to 3.39 ± 3.23 ml/min/1.73 m^2, P = ns). The study suggested that RKF was better preserved in PD patients on la ow-protein diet supplemented with keto-acids.

In the prospective cohort study by Johnson et al. each 1 g/kg body weight/day increase in dietary protein consumption was found to be associated with an adjusted hazard ratio of 2.87 (9% CI 1.01 to 2.72, $P < 0.05$) for RKF loss [85].

In low certainty evidence, dietary modification in terms of reduced protein intake with keto-acid supplementation may help preserve RKF in PD patients.

Diuretics

In a small 12-month randomized controlled trail (RCT) of 61 patients, furosemide at a dose of 250 mg per day was found to significantly increase urine volume over 12 months (+48.8 ml/24 hours) compared to a decline (−305 ml/24 hours, $P < 0.05$) in the no furosemide group [8]. However, the decline in creatinine and urea clearance was similar in both groups. Some cohort studies noted diuretic use to be associated with a more rapid decline in RKF [95, 96]. In low certainty evidence, furosemide may make little or no difference to RKF preservation.

Other Factors

Despite the lack of evidence in dialysis patients, avoidance of nonsteroidal anti-inflammatory drugs or any other known nephrotoxins in patients with RKF would seem prudent.

If there is a significant decline in RKF that cannot be explained, consideration should always be given to the possibilities of volume depletion or obstruction, as these are easily correctable causes of loss of RKF.

Conclusions

Our understanding of the effect of PD adequacy on outcomes is subject to the limitations of the existing literature. In the absence of a "gold standard" for assessing clearance, all studies to date have focused on small solute clearance. This has led to a relative neglect of the impact of middle molecule clearance on outcome. The data presented in this chapter highlight the relative contributions of kidney and peritoneal clearance to PD adequacy, demonstrating that maintenance of residual kidney clearance is strongly associated with patient survival. It is not yet clear if this association is related to improved volume

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Table 45.14 Summary of studies assessing the effect of aminoglycoside use on RKF in PD patients.

Study	Study design	No. of patients	Follow-up	Interventions	Outcome measure	Result
Lui 2005 [9]	RCT	50	6 weeks	Cefazolin plus netilmicin vs. cefazolin plus ceftazidime	End of study RKF compared to baseline values	Mean RKF 4.25 ml/min vs. 4.16, $P = 0.79$ for the netilmicin group and mean RKF 4.00 ml/min vs. 3.90 ml/min, $P = 0.76$ for the cefazolin plus ceftazidime group
Singhal 2000 [11]	Prospective	242	27 months	Aminoglycoside >5 days vs. none	Slope of RKF decline	Slope of RKF decline reported to be significantly steeper in those who received aminoglycosides ($P = 0.0006$)
Baker 2003 [12]	Prospective	205	<6 months	Gentamicin vs. none	Decline in RKF	0.08 ml/min/month in PD peritonitis patients treated with the gentamicin-based regimen compared with 0.17 ml/min/month in the group without gentamicin Authors report no significant difference between either group
Shemin 1999 [10]	Prospective	72	14 months	Aminoglycoside >3 days vs. none	Decline in RKF	Significantly higher in gentamicin group than in those who did not receive gentamicin (0.66 ml/min/month vs. 0.21 ml/min/month, $P < 0.01$)
Badve 2012 [13]	Retrospective	2715	4916 patient-years	At least one course of aminoglycoside	Slope of RKF decline	Similar in patients treated and not treated with at least one course of aminoglycoside Median (IQR range) −0.26 (−1.17 to 0.04) ml/min/1.73 m^2/month vs. −0.22 (−1.11 to 0.01) ml/min/1.73 m^2/month, $P = 0.90$

IQR, interquartile range; PD, peritoneal dialysis; RCT, randomized controlled trial; RKF, residual kidney function.

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Table 45.15 Summary of findings: effect of netilmicin (aminoglycoside) + cefazolin versus ceftazidime + cefazolin for PD peritonitis on RKF.

Netmicin + cefazolin versus ceftazidime + cefazolin					
Outcomes	**No. of participants (studies)**	**Assumed risk**	**Corresponding risk**	**Quality of the evidence (GRADE)**	**Conclusion**
Residual kidney function ml/min/1.73 m^2	36 (one RCT)	Mean RKF in control (ceftazidime + cefazolin) group was 4.16	Mean RKF in netilmicin + cefazolin group was 0.25 lower (1.65 lower to 2.15 higher)	⊕⊕⊖⊖ Low	There may be little or no difference between aminoglycoside vs. no aminoglycoside containing antibiotic regimens for treatment of PD peritonitis with respect to RKF
Urine volume ml/day	36 (one RCT)	Mean daily urine volume/day in control (ceftazidime + cefazolin) group was 799	Mean daily urine volume in netilmicin + cefazolin group was 29 higher (316 lower to 374 higher)	⊕⊕⊖⊖ Low	There may be little or no difference between aminoglycoside vs. no aminoglycoside containing antibiotic regimens for treatment of PD peritonitis with respect to daily urine volume

PD, peritoneal dialysis; RCT, randomized controlled trial; RKF, residual kidney function.

management and middle molecule clearance, or if it is merely an association, with RKF serving a marker of a healthier population.

Based on moderate certainty evidence, increasing *Kt*/*V* beyond 1.7 does not appear to have an impact on patient survival. Weekly *Kt*/*V* levels below 1.7 may be associated with an increased risk of death (low certainty evidence), although a minimum total weekly *Kt*/*V* target has not been definitively established. Even though there is not yet sufficient evidence regarding the effect of middle molecule clearance on survival in PD patients, it would be prudent for efforts to improve peritoneal clearance to address both small and middle-molecule clearances. Furthermore, the true adequacy of PD as a form of kidney replacement therapy depends not only on successful clearance of uremic toxins, but also on adequate volume management through a combination of peritoneal ultrafiltration and residual urine volume. There is an increasing realization that the assessment of dialysis adequacy should be multidimensional and should include other important parameters such as patient reported outcomes [97]. These concepts underpin the current ISPD guideline on optimal PD prescription which now recommends that clinicians not use small solute clearance measures alone to make important clinical decisions such as PD prescription and modality switches [59].

In low to very low certainty evidence, PD modality, diuretic, and aminoglycoside use may have little or no impact on RKF. However, given the survival advantage that is associated with kidney clearance, every effort should be made to preserve RKF with neutral pH, low GDP solutions, the avoidance of potential nephrotoxins, the use of agents with potentially protective effects, and a search for reversible etiologies when a decline in RKF is noted.

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46

Salt and Water Balance

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Introduction

Achieving salt and water balance is fundamental to optimizing fluid status, one of the key objectives of peritoneal dialysis (PD) treatment. Excess salt and water, accumulating in the intravascular and extravascular extracellular spaces, cause hypertension and target organ damage (e.g. increased left ventricular mass, stroke), pulmonary oedema, and oedema of other tissues (laryngeal, gut, lower limb, anasarca), which can affect organ function and contribute to morbidity and mortality [1–5]. Conversely, negative salt and water balance can be a reflection of reduced nutrition, reflecting poor intake [6, 7], or accelerated losses in residual kidney function if due to excessive salt and water removal [8, 9]. Achieving appropriate salt and water balance is an important balance for clinicians.

The relative importance of salt and water management to patient outcomes was historically underestimated by early treatment guidelines, which tended to focus on small solute clearance as the principal metric of dialysis adequacy. The realization that the survival benefits of small solute clearance mainly reflect the component attributable to residual kidney function, combined with increasing evidence that inherent differences in peritoneal membrane function that potentially affect salt and water removal has led to a paradigm shift, with increasing emphasis on fluid status. However, optimal management of salt and water balance is a complex problem and decisions made by clinicians often represent a compromise between attempts to normalize fluid status while taking additional factors, notably comorbidity and hypoalbuminemia, into account. It is possible to divide the components of this complex process and the limited evidence to support decision-making into two broad components: (i) interventions designed to influence salt and water balance (e.g. dietary salt intake, prescriptions that optimize fluid removal) and (ii) interventions designed to guide clinical decision-making through accurate ascertainment of fluid status (e.g. bioimpedance) (Table 46.1).

Definitions

Optimal salt and water balance might be defined as the input and output which enables an individual to achieve a stable and normal body composition, and includes normal extracellular (intra- and extravascular) fluid volumes (also referred to as the normally hydrated weight), as well as maintaining healthy lean and fat tissue masses. The main problem with this definition is that there are other factors which influence this optimal goal [10]. For example, muscle wasting is very common in dialysis patients and yet in the absence of kidney failure this is often associated with a relative excess in the hydrated weight even though the total water volume of the patient is reduced. Reducing salt and water intake in this context is unlikely to benefit the underlying problem of muscle wasting unless it can be linked to increased calorie intake.

There is, as yet, no evidence-based practice that tells the clinician how to take these additional factors into account, although it can be envisaged in the future it will be possible to take a stratified approach to defining the optimum body composition goal for a given degree of comorbidity, muscle wasting, and hypoalbuminemia. Currently, this is based on best clinical judgment. The potential role of bioimpedance to guide fluid management is discussed below.

Another definition that is required is the conditions in which no amount of clinical intervention will solve the problem of salt and water balance, i.e. ultrafiltration insufficiency. While this occurs in a minority of patients, usually a problem that is either revealed by the loss of residual kidney function or because of acquired peritoneal membrane injury, it is an important cause of technique

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Table 46.1 Salt and water balance.

Treatment	Recommendation	Certainty of evidence	Strength of recommendation
Dietary advice on salt intake	We suggest that salt intake can be reduced to ≤6 g/day to lower blood pressure and improve fluid balance. Patients receiving PD may reasonably choose not to accept this level of salt restriction based on the very low certainty evidence that treatment makes a difference to longer term outcomes, including quality of life and mortality, and very low certainty evidence that very low salt intake (<4 g/day) may lead to malnutrition.	Very low	Weak
Diuretics (high-dose furosemide)	We suggest that furosemide can be prescribed in a dose of 250 mg daily to increase urine output.	Low	Weak
APD	We suggest that APD can be prescribed to increase peritoneal ultrafiltration, particularly in patients with rapid solute transfer in whom APD may also reduce mortality.	Very low	Weak
Glucose polymer (Icodextrin)	We suggest that glucose polymer solution can be used to increase daily ultrafiltration and reduce uncontrolled fluid overload in peritoneal dialysis patients. PD patients may reasonably choose not to use glucose polymer as treatment makes no difference to hard outcomes, including technique survival and mortality.	Moderate: Net daily ultrafiltration, uncontrolled fluid overload and improved extracellular fluid volume Low to very low: Residual renal function, urine volume, rash, peritoneal creatinine clearance, peritonitis, technique survival, and mortality	Weak
Bioimpedance-guided fluid management	We suggest that bioimpedance-guided clinical fluid management can be used to improve fluid status and blood pressure. Patients receiving PD may reasonably choose not to receive bioimpedance-guided clinical fluid management based on very low certainty evidence that such treatment makes any difference to longer term outcomes such as quality of life or mortality.	Low	Weak

APD, automated peritoneal dialysis; PD, peritoneal dialysis.

failure in long-term PD patients [11]. It is also a risk factor for encapsulating peritoneal sclerosis (EPS) [12]. Ultrafiltration insufficiency can be defined strictly from membrane function tests (see section "Diagnostic Tests"), but there are relative definitions applied in clinical practice, for example an inability to maintain optimal salt and water balance without an unacceptable amount of glucose peritoneal exposure.

Epidemiology

Evidence that Salt and Water Balance is Important

Ultrafiltration insufficiency, although relatively uncommon, is strong evidence that a failure of adequate salt and water balance can be a modality-limiting factor for patients on PD. Uncommon in the early stages of treatment (affecting <10%) and potentially masked by persisting residual kidney function, the incidence rises to ~25% after 5 years of treatment [11, 12]. Ultrafiltration insufficiency is, however, one end of the severity spectrum and various degrees of less efficient salt and water removal may be contributing to mortality on PD before it is formally recognized, prior to necessitating dialysis modality switch (see Table 46.2). The European Automated Peritoneal Dialysis Study (EAPOS) suggests this is the case. A nonrandomized cohort study of automated peritoneal dialysis (APD) to treat anuric PD patients, with pre-agreed intervention targets for both solute clearance and fluid removal (>750 ml ultrafiltration per day) found that failure to reach the fluid target was associated with lower survival, partly explained by having less efficient membranes [13, 17]. This is supported by a similar analysis of anuric PD patients from the Netherlands Cooperative Study of Adequate Dialysis (NECOSAD) in

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Table 46.2 Ultrafiltration and sodium removal/intake and survival.

Outcomes	Source	No. of participants (no. of studies)	Adjusted relative risk (95% CI)	Certainty of evidence	Conclusion
All-cause mortality	**EAPOS** [13]	**177 (multicenter, anuric)**	0.45 (0.18, 0.97)[a]	Moderate •••	Salt and water removal independent of residual kidney function is associated with better survival
	NECOSAD [14]	*Per l ultrafiltration*			
	ADEMEX [15]	**130 (multicenter, anuric)**	0.48 (0.23, 0.97)[b]		
		Per l ultrafiltration			
	Ates et al. [16]	**965 (multicenter trial)**	1.53 (1.175, 1.995)[c]		
		Ultrafiltration <400 ml	0.93 (0.89, 0.969)[c]		
	Dong et al. [6, 7]	*Per 100 ml urine volume*			
		125 (single center)	0.9 (0.84, 0.96)[d]		
		Per 100 ml fluid removal	0.9 (0.84, 0.96)[d]		
		Per 10 mmol sodium removal			
		305 (single center)	0.45 (0.23, 0.90)[e]		
		Per g dietary sodium	0.83 (0.7, 1.00)[f]		
		Per g total sodium removal			
Cardiovascular mortality	**Dong et al.** [6]	**305 (single centre)** Per g dietary sodium	0.33 (0.1, 1.1)[e]	Very low •	Too few studies have reported on this subgroup to comment
Technique survival	**NECOSAD** [14]	**130 (multicenter, anuric)** Per l ultrafiltration	1.13 (0.59, 2.14)[b]	Very low •	Too few studies have addressed this outcome to comment

[a] Adjusted for age, gender, comorbidity, time on dialysis, solute transfer rate, and subjective global assessment.
[b] Adjusted for age, comorbidity, subjective global assessment, time on dialysis, albumin, and hemoglobin.
[c] Adjusted for age, comorbidity, albumin, protein nitrogen appearance, inflammation, and pro-brain naturetic peptide.
[d] Adjusted for comorbidity, serum creatinine, and residual kidney clearance.
[e] Adjusted for age, gender, BMI, comorbidity, baseline mean arterial pressure, hemoglobin, albumin, calcium, phosphate, LDL, solute clearances, and C-reactive protein.
[f] Time-dependent sodium removal adjusted for age, comorbidity, and time-dependent solute transfer rate (which was a strong predictor of mortality in the model).

which anuric patients with less than 1 l of ultrafiltration had worse survival [14]. Whether the reduced ultrafiltration is a marker of membrane dysfunction or a reflection of low nutritional intake, this is evidence that salt and water balance may be of greater immediate importance than peritoneal solute clearance in anuric patients.

Peritoneal Solute Transport Rate and Outcomes

There is now a large body of evidence to suggest that peritoneal membrane function, specifically the rate of peritoneal solute transfer, which varies quite considerably between patients, is an important determinant of survival on PD. The rate of small solute transfer diffusion across the membrane is inversely associated with survival, as demonstrated by several single-center studies [7, 11, 18], a systematic review [19], and large multicenter cohorts, such as the Canada-USA (CANUSA) study [20], the Australian and New Zealand Dialysis and Transplant (ANZDATA) Registry [21], the Davita Database [22], and prevalent patients in the Global Fluid Study [23] (summarized in Table 46.3). There is no conclusive evidence that faster solute transfer leads to technique failure, although in the Davita database it was associated with an increase in hospitalization events [22]. It is important to note that the increased risk extends across the range of solute transfer and is not limited to just very fast transfer (i.e. ratio >0.8).

Blood Pressure and Salt and Water Balance

Hypertension is common in PD patients and, given the high cardiovascular morbidity and mortality in dialysis patients, it is a crucial aspect of patient management. Despite this, the evidence linking salt and water balance to blood pressure and blood pressure to survival in PD is of low certainty. Bioimpedance studies would indicate that whereas overhydration in PD patients is common, this is only associated with poor blood pressure control in about half of these patients and conversely hypertension was observed in over one-third of the normo-volaemic patients [24]. Longitudinal studies have suggested that blood pressure is relatively good

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Table 46.3 Adverse outcomes associated with faster peritoneal transport rate.

Outcomes	Source	No. of participants (no. of studies)	Adjusted relative risk (95% CI) per 0.1 increase in D/P creatinine	Certainty of evidence (GRADE)	Conclusion
All-cause mortality	**Brimble et al. meta-analysis** [19]	6648 (19 studies, includes CANUSA study and ANZDATA Registry)	1.15 (1.07, 1.23)	High ••••	Mortality risk increases with increasing peritoneal transport rate
	Global Fluid Study [23]	Incident cohort, 499 Prevalent cohort, 307 (one study, 10 centers)	1.1 (0.98, 1.23) 1.18 (1.003, 1.41)		
	Davita database [22]	10 142 (one study, 764 centers)	1.07 (1.02, 1.13)		
	Pooled		**1.11 (1.05, 1.17)**		
Technique failure (death censored)	**Brimble et al. meta-analysis** [19]	5104 (six studies)	1.18 (0.96, 1.46)	Low •	No evidence of increased risk of technique failure
	Davita database [22]	As above	1.01 (0.98, 1.05)		
	Pooled		**1.04 (0.92, 1.16)**		
Hospitalization	**Davita database** [22]	As above	1.05 (1.03, 1.06)	Moderate ••	Increased solute transfer rate probably leads to more frequent hospitalization

in the early years of PD, but once residual kidney function has diminished this becomes more difficult to control, indirectly implicating a role for worse salt and water balance in blood pressure management [2]. However, it should be remembered that blood pressure may also be influenced by increasing arterial stiffness related to increasing vascular calcification over time. It has been demonstrated that blood pressure control can be achieved by reducing salt intake and increasing ultrafiltration after antihypertensive drug withdrawal, confirming a short-term association, but it is not clear that this is the correct treatment strategy and the intervention did result in a significant and relatively rapid decline in residual kidney function [9]. Sodium removal can also be increased by using a low sodium containing dialysate and this has led to modest reductions in blood pressure in two intervention studies, providing further modest evidence that blood pressure can be improved by manipulating salt and water balance [25, 26]. However low sodium solutions are not currently commercially available and cannot be considered as a treatment option.

Studies show that, as for hemodialysis patients, the relationship between blood pressure and survival is complex, exhibiting reverse epidemiology (U-shaped relationship to survival) [27, 28] that likely explains at least in part the poor correlation between fluid status and blood pressure as a consequence of poor cardiac function [29]. Poor control of high blood pressure in patients on the transplant waiting list is associated with worse long-term survival [27].

Compared to hemodialysis, the evidence base for pharmacological interventions to improve blood pressure control is very modest, with studies limited to renin-angiotensin system blockade and in half these studies the primary outcome was preservation of residual kidney function [30–32]. Although these trials overall give a weak signal of benefit, suggesting that decline in kidney function and progression of left ventricular mass are slowed, they have small sample sizes and limited conclusions can be drawn.

Pathophysiology

Peritoneal Membrane Function

Given the importance of the peritoneal membrane in facilitating salt and water balance, the considerable degree of individual variation in membrane function, and the strong association of membrane function with patient survival, it is important that membrane physiology is well understood. The three-pore model developed by Rippe and colleagues remains the best tool for this [33, 34], with its ability to explain free water transport via the aquaporin pathway, predict sodium removal [35], show how polyglucose solutions can work [36], and provide a mechanistic understanding of fluid reabsorption via Starling forces [37], providing an overall theoretical framework.

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Physiology of Small Solute Transport

Applying this model to explain why a fast solute transfer rate might lead to worse outcomes shows how this will impair salt and water removal by two mechanisms. First, the more rapid transport of glucose from the peritoneal cavity to the circulation will lead to a faster reduction in the osmotic gradient and thus more rapid reduction in the ultrafiltration rate. Second, once there is osmotic equilibration across the membrane, which happens earlier in individuals with rapid transfer, there will be back flow of salt and water into the circulation driven by Starlings forces that will be more severe because these individuals effectively have larger membranes. The three-pore model shows that the anatomical structure (or pore) responsible for small solute transfer is the intercellular tight junction between endothelial cells, so membrane size here refers to the capillary circulation in contact with dialysate rather than the physical size of the membrane. It is now clear that the most important determinant of individual variation in solute transfer rate is due to local inflammation within the membrane, determined by the local production of inflammatory cytokines, most notably IL-6 [23]. This is independent of systemic inflammation, which is more closely aligned to age and comorbidity. Thus, the possibility that high solute transfer mediates its effects on survival through an association with systemic inflammation, as was once thought, may be incorrect, further emphasizing the importance of salt and water balance.

Physiology of Fluid Transport and Ultrafiltration Failure

Although fast peritoneal solute transfer causes reduced salt and water removal by these mechanisms, patients with ultrafiltration insufficiency usually have the additional problem of reduced membrane efficiency. For the same osmotic gradient across the membrane they ultrafiltrate less, referred to as a reduction in the osmotic conductance of the membrane. Typically, this is a problem that is acquired with time on treatment [38, 39] and the pathophysiology is characterized by progressive fibrosis of the membrane and, in particular, by a vasculopathy [40]. A modification of the three-pore model in which a fiber matrix is placed in series with the capillary endothelium shows how this can impede water flow (and thus convective salt removal) even when the capillary surface area is increased [34]. Drivers of this progressive fibrosis of the membrane include glucose and other non-biocompatible components of dialysis fluid (osmolality, glucose degradation products, pH), local inflammation, and infection [41]. It is theoretically possible that there are other mechanisms responsible for the reduction in osmotic conductance, such as a reduced aquaporin expression. Aquaporins, responsible for about 50% of ultrafiltration (free water transport) [37, 42], are essential for peritoneal dialysis to work. However, in patients with severe acquired membrane failure aquaporin expression is still present whereas the presence of fibrosis is often extreme [40].

There is another important consequence of the presence of the free water aquaporin pathway. While it is essential to ensure that adequate ultrafiltration is achieved, it does mean that the sodium concentration in ultrafiltrate is always less than that of plasma. At the start of a hyperosmolar exchange there is a fall in the sodium concentration of dialysate due to water crossing via the free water pathway, a process often referred to as sodium sieving [33, 35]. This fall or dip in the dialysate sodium, which can typically be 10 mmol/l, takes time to equilibrate but does mean that for a typical continuous ambulatory peritoneal dialysis (CAPD) regimen the sodium removal is 100–110 mmol/l ultrafiltrate and for a typical APD regimen it is 70–80 mmol/l over a 24-hour period. This has implications for balancing salt and water intake with output when designing the optimal dialysis regimen.

Hypoalbuminemia and Fluid Status

PD is associated with hypoalbuminemia for several reasons, including peritoneal protein losses, systemic inflammation, and malnutrition. The most important of these is peritoneal protein loss, which is associated with a faster peritoneal transport rate. While this may not affect salt and water balance directly, every study examining the relationship between bioimpedance-determined fluid status and serum albumin levels so far published has found a negative correlation which likely contributes to salt and water retention occurring as membrane transport rate increases [24, 43, 44]. Isotopic studies have shown that the overhydration associated with hypoalbuminemia is not correlated with plasma volume, which is normal in PD patients, implying that it increases the extravascular extracellular fluid compartment [45]. Increasing salt and water removal may benefit this and should be considered when there is a risk of pulmonary or laryngeal oedema. However, care should be taken not to centrally deplete the patient too rapidly if residual kidney function is present. As in hemodialysis patients, hypoalbuminemia is a predictor of worse survival but there is no compelling evidence to indicate that it is a reason for switching dialysis modality at present [46].

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Diagnostic Tests

Evaluation of Peritoneal Membrane Function

The peritoneal equilibration test (PET) was developed to assess two aspects of peritoneal membrane function, the rate of small solute transfer determined from the dialysate: plasma creatinine ratio and the net ultrafiltration capacity [47]. It requires standardized conditions (4 hours duration, glucose concentration, dwell volume) and standardized measurements (calculation of net ultrafiltration volume that accounts for the variable overfill of dialysis bags and use of laboratory assays that either measure creatinine directly or account for the presence of glucose, which can interfere with some methods, e.g. Jaffe method). Even taking these precautions into account, studies that have included data from multiple sites have found a center effect in the measurement of solute transfer which means that direct comparisons of absolute values should be made with care and preferably after establishing the mean value and distribution in the local population (solute transfer rate is normally distributed).

Solute Transfer Rate: Reproducibility and Diagnostic Value

Expressed as the dialysate:plasma ratio of creatinine at 4 hours, the range is 0.3–1.1, with a typical mean value of 0.67. The coefficient of variation is about 10% when measurements are taken close together so a change in >0.1 should be considered clinically meaningful. It is independent of the glucose concentration used (provided assays correct for glucose interference if needed). Over time, there may be fluctuation in the peritoneal transport rate in any one individual, likely reflecting variations in local membrane inflammation. At a population level over several years, the solute transfer rate tends to increase [39, 48]. The primary diagnostic value is in identifying individuals at the high end of the range as this is a predictor of adverse outcomes, worse survival, possibly technique failure, and hospitalization (see Table 46.3). This should prompt the clinician to make prescription changes if needed. The other main clinical use of the solute transfer measure is in designing the optimal dialysis prescription schedule for solute clearance. Slow transfer membranes require longer dwell lengths to optimize larger molecule clearance (e.g. phosphate).

Ultrafiltration Capacity: Reproducibility and Diagnostic Value

The net ultrafiltration capacity at 4 hours using a 2-l exchange (this volume is adjusted in children according to size) represents the composite of a number of processes, including the amount of ultrafiltration that has occurred through the two main pathways less the fluid reabsorption that occurs via Starlings forces and "lymphatics." Despite the number of mechanisms involved, it is the key metric for defining ultrafiltration insufficiency. A strict membrane definition is <400 ml net ultrafiltration using a 3.86% glucose concentration or <100 ml using a 2.27% glucose concentration (values exclude any overfill of the dialysis bag) [49].

It is important, however, that these values are derived and interpreted in context. The reproducibility of the drained dialysate volume is more than for solute transfer, with a coefficient of variation close to 25%, and can be worse in a patient with catheter drainage problems. Indeed, on obtaining a low net ultrafiltration volume while undertaking a peritoneal equilibration test, it is most appropriate to ensure catheter function is adequate.

The main value of this test is in helping to determine whether membrane function is contributing to a failure to maintain salt and water balance. It should be done when there is clinical evidence of problems, including poor overall ultrafiltration, a need for excessive glucose usage to maintain fluid balance, and evidence of excess salt and water retention such as hypertension, oedema, or worsening bioimpedance measurements. Given that ultrafiltration insufficiency is a risk factor for subsequent EPS, it also has a role in deciding whether PD treatment should be continued after a number of years [12].

Adding the Sodium Dip: Additional Value

The standard PET has limitations, especially when it comes to distinguishing *true* poor ultrafiltration from catheter dysfunction or identifying when the cause of ultrafiltration insufficiency is due to reduced membrane efficiency (*osmotic conductance*) as opposed to just rapid solute transfer. The most comprehensive way of doing this is to undertake a double mini-PET which involves doing two back-to-back 1-hour tests using a weak (1.36%) followed by a strong (3.86%) glucose exchange [50, 51]. The value of using two different glucose concentrations is that the difference in ultrafiltration obtained between them is a measure of the osmotic conductance (see Box 46.1). A patient with a low osmotic conductance as a cause for ultrafiltration insufficiency should be transferred to hemodialysis (unless otherwise inappropriate) as it is unlikely to be possible to achieve satisfactory salt and water balance and there is a risk of future EPS. However, the double mini-PET is quite labor intensive and still subject to the error associated with measuring drain (ultrafiltration) volumes, especially when there is a large residual volume within the peritoneum at the end of the dwell [52].

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Box 46.1 Advanced Testing of Membrane Function (Osmotic Conductance, Sodium Dip, and Sieving)

	Example value *(normal value)*		Diagnostic value
PET glucose concentration	PET1: 1.36%	PET2: 3.86%	
Net ultrafiltration (UF) at 1 h (ml)	260	615	
Osmotic conductance (μl/min/mmHg)	3.75 *(>1.85)* [51]		Diagnoses ultrafiltration insufficiency that will not be solved by prescription (e.g. APD, icodextrin) in anuric patients
D/P creatinine at 1 h	0.36	0.32	
MTAC creatinine (ml/min)	5.2		
Dialysate sodium (mmol/l) at 1 h	129	122	
Sodium dip, mmol/l (131-[$Na_{3.86\%}$] at 1 h)	9 *(8.4, IQR 6–11)* [53, 54]		Normal values established from 758 incident patients. Low value was the best membrane function discriminator for EPS (added to age, time on treatment, and solute transfer) based on 161 long-term patients of which 13 developed EPS
Sodium sieving ratio (1-([$Na_{3.86\%}$]/131) at 1 h)	0.068 (>0.06) [40]		Based on 35 long-term (matched) patients, seven with EPS <0.03, associated with 50% risk of EPS which equates to a sodium dip <5

Definitions and calculations:

Osmotic conductance (OC) is the fluid removed per minute per osmotic gradient due to glucose, calculated fwrom the difference in ultrafiltration (UF) obtained at two glucose strengths. Values <1.85 indicate severe ultrafiltration insufficiency, >4 well preserved UF.

$$OC = 1700 \times \left(\text{UFv}3.86\% - \text{UFv}1.36\%\right) / \left(1158 \times \left(\frac{3.86}{0.018}\right) - \left(\frac{1.36}{0.018}\right)\right)$$

D/P, dialysate: plasma ratio; MTAC, mass transfer coefficient (for creatinine), the rate of creatinine diffusion across the membrane, calculated as:

$$\text{MTAC} = \left(\text{UFv}3.86\% / 60\right) \times \ln\left(\left(2000 \times \left[\text{plasma creatinine}\right]\right) / \left(\text{UFv} \times \left(\text{plasma} - \text{dialysate creatinine}\right)\right)\right)$$

A simpler solution is just to measure the sodium dip at 1 hour using a single 3.86% exchange. This gives a good estimate of the ultrafiltration due to free water transport at 1 hour that is not dependent on precise measurement of the ultrafiltration volume (see Box 46.1). There is also evidence that this is a better predictor of future EPS than ultrafiltration volume alone [40, 53].

Bioimpedance

Prognostic Value

Bioimpedance is increasingly used to assess body composition in dialysis patients. By passing a weak, unfelt alternating current between the extremities of the upper and lower limbs, it is possible to measure both tissue resistance and reactance. Resistance is inversely proportional to body water whereas reactance is proportional to the impedance of cell membranes and thus an indicator of tissue mass [55]. All bioimpedance devices use this information to model the body composition, typically using population-derived equations that then estimate the volume of tissue compartments with varying degrees of sophistication. Regardless of how sophisticated these methods are, the relationship of reactance to resistance (cell mass to total body water) is key to the prognostic value of this test. A reduction in this ratio will reflect both overhydration and reduced muscle mass to varying degrees and is strongly predictive of worse survival. In a meta-analysis of 38 dialysis cohort studies that undertook multivariate analyses adjusting for confounders, such as age and comorbidity (including 10 in PD patients), all but one estimated that bioimpedance measurements of overhydration was an independent predictor of worse survival [44]. In a subgroup meta-analysis, overhydration >15% (hazard ratio [HR] 2.28, 95% confidence interval [CI] 1.56–3.34) or a 1° decrease in the phase angle (HR 1.74, 95% CI 1.37–2.21) was associated with increased mortality. In two very large hemodialysis cohorts the increase in mortality was additive to inflammatory status and blood pressure at whatever level of the U-shaped survival relationship [56, 57].

Although these data demonstrate the prognostic value of bioimpedance, it is important to recognize that the mortality association with excess salt and water may not be amenable to changes in salt and water balance in all situations. Illness of whatever cause, especially when there is muscle wasting and poor nutrition or frailty [58], is associated with a relative

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increase in tissue hydration for a given muscle mass, which may account for a substantial part of this association but is hard to change through clinical interventions.

Guidance of Salt and Water Balance

Given the predictive value of bioimpedance, it is natural to ask if it can be used to guide and thus improve fluid management in dialysis patients. Two recent meta-analyses have assessed the limited trial literature [59, 60], in both cases including both hemodialysis (HD) and PD studies. The first of these limited its scope to trials using multifrequency bioimpedance and was undertaken for the National Institute for Health and Care Excellence (NICE) and is published alongside their guidance [61]. Since publication of these meta-analyses, one further trial in PD has been published [62]. Overall, the conclusions were limited to beneficial effects on maintaining or improving fluid status absolute reduction in overhydration (mean difference −0.39 l [−0.62, −0.15] [59] or −0.43 l [−0.71, −0.15] [63]) and lower systolic blood pressure (mean difference −2.73 mmHg [−5.00, −0.46] [63]). So far, trials have not been powered to determine the effects of bioimpedance-guidance of salt and water balance management on mortality or cardiovascular events. To date, only three trials [62, 64, 65] have been undertaken in PD patients (although one had four nested subgroups) [65] and these are summarized in Table 46.4. They were heterogeneous in their approach but there were some common features. Fluid status was stable over 12 months in the control groups of nonanuric patients (both countries in the UK–Shanghai trial, [65] COMPASS trial [62]). In the active limb for nonanuric patients, clinicians were either reluctant to intervene to target or, when they did by setting a lower target weight without changing the dialysis prescription, there was no change in fluid status. In the Shanghai anuric subtrial, body composition did deteriorate in the control group, mainly as a function of losing muscle mass, and this was prevented in the active limb. At present, there is insufficient evidence to guide the use of bioimpedance-guided fluid management as part of routine clinical practice [66].

Treatment

Dietetic Advice on Salt Intake

In advising an appropriate salt intake for subjects on PD, three things need to be taken into account: (i) given the high prevalence of hypertension and its complications, there should be a modest restriction applied as recommended for all such individuals (given there is no specific evidence for this patent group) [67], (ii) salt intake should match achievable removal so as to make balance possible, and (iii) salt restriction should not compromise good nutrition.

If salt and water balance is to be achieved, then salt intake must be matched to an achievable output but at the same time not prohibit adequate nutritional input. For example, in an anuric patient on PD, it is reasonable to aim for a daily ultrafiltration of around 1 l. This would equate typically to 100 mmol of sodium per day (or 6 g of salt) for a CAPD patient and 80 mmol (5 g of salt) for an APD patient, but this should be measured in individuals if in doubt. This is close to the current recommendations for people with hypertension [67] and should be achievable while maintaining adequate nutrition. There are no trials of different levels of salt intake in PD on which to base a tested recommendation but cohort studies which measured sodium intake, or inferred this from sodium removal, are summarized in Table 46.2. These generally show that survival is associated with higher sodium removal and in particular a low sodium removal is associated with poor survival. Regardless of the direction of causality, or the role of membrane function, restricting salt intake to less than 5 g per day does not appear to be justified and may be problematic in terms of maintaining adequate nutrition. Patients on PD may infrequently have very high ultrafiltration volumes and can lose excessive amounts of salt. This may be exacerbated if they also have a salt-losing nephropathy as the cause of their renal failure. Limiting the number of dialysis exchanges or using very long dwells with a low glucose concentration can encourage net salt and water reabsorption as well as encouraging salt intake.

Use of Diuretics

A number of studies have been undertaken with diuretics in PD patients, summarized in Table 46.5. Taken together, there is modest evidence that furosemide can maintain urine volume and possibly delay time to anuria [68, 69]. In one of these studies, this was associated with a higher sodium excretion than controls [68]. Whether this translates into a patient-level benefit is uncertain, although in principle it should mean that there is less need to achieve higher peritoneal ultrafiltration, thereby sparing intraperitoneal glucose administration. There is no evidence that it benefits blood pressure or fluid status, although total body water was a lower proportion of body weight in patients randomized to furosemide. It should be noted that the typical amount of sodium removed per liter of urine is usually significantly less than per liter of ultrafiltrate. Studies of aldosterone antagonists (e.g. spironolactone) are more numerous but have mainly focused on outcomes other than salt and water balance [70–72]. None that measured urine volume or sodium excretion reported any effect (Table 46.5).

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Table 46.4 Summary of bioimpedance-guided fluid management studies in PD.

Outcomes	Source	No. of participants (bioimpedance measure)	Effect (95% CI)	Certainty of evidence	Conclusion
Fluid status (overhydration, L or ECW/TBW ratio)	**Luo et al.** [64]	160 (overhydration at 3 m, l)	−0.80 L (−1.32, −0.28)	Very weak •	No consistent effect seen Volume status was very stable in the nonanuric subjects and clinicians made no significant prescription interventions for volume management in active or control nonanuric subjects
	Tan et al. [65]	131 UK, nonanuric (ECW/TBW at 12 m)	0.00 (−0.03, 0.03)		
	Tan et al. [65]	84 Shanghai, nonanuric (ECW/TBW)	0.01 (−0.02, 0.04)		
	Tan et al. [65]	75, Shanghai, anuric (ECW/TBW)	−0.03 (−0.08, 0.02)		
	Oh et al. [62]	137 (overhydration, at 12 m, l)	0.001 (−0.59, 0.59)		
Systolic blood pressure (mmHg)	**Luo et al.** [64]	160	−6.17 (−12.66, 0.32)	Weak •	Although an overall reduction in blood pressure is seen, especially in nonanuric patients, given the lack of changes in prescriptions or change in fluid status this raises the possibility of alternative explanations of the observed effect (e.g. performance bias)
	Tan et al. [65]	131 UK, nonanuric	−4.00 (−12.18, 4.18)		
	Tan et al. [65]	84, Shanghai, nonanuric	−5.00 (−13.92, 3.92)		
	Tan et al. [65], **Oh et al.** [62]	75, Shanghai, anuric	5.00 (−9.2, 19.2)		
		137	−6.3 (−13.76, 1.16)		
	Pooled		**−4.75 (−8.42, −1.09)**		
Residual urine volume	**Luo et al.** [64]	160	−98.5 ml (−204, 7)	Very weak •	The suggestion of an effect is dominated by the Luo study with just 3 months of follow up
	Tan et al. [65]	131 UK, nonanuric	−147 ml (−363, 69)		
	Tan et al. [65], **Oh et al.** [62]	84 Shanghai, nonanuric	163 ml (−157, 483)		
		137	−23 ml (−356, 300)		
	Pooled		**−84.4 (−169, 6.1)**		

ECW/TBW, ratio extracellular water:total body water, a 0.03 change is equivalent to 1 l change in relative extracellular water volume.

Table 46.5 Summary of trials using diuretics in peritoneal dialysis.

Outcomes	Source	Intervention (no. of participants)	Effect (95% CI)	Certainty of evidence	Conclusion
Urine volume and sodium excretion	**Medcalf** [68]	Furosemide 250 mg/day [64]	29.7 (0.19, 59)	Weak ••	Possible beneficial effect of furosemide maintaining urinary volume and sodium removal without benefiting solute clearance
		Difference in urine volume (ml/month)	3.29 (0.12, 6.45)		
		Difference in urinary sodium (mmol/month)	−0.049 (−0.17, 0.07)		
		Difference in creatinine clearance (ml/min/month)			
	Flinn et al. [69]	Furosemide (61, 20 treated, 41 matched controls)	25.7 (−39.7, 91.2)	Very Weak	
		Difference in decline of urine volume at 12 m (ml)	5% on frusemide vs. 22% controls became anuric		
	Ito et al. [70]	Spironolactone, 12.5–25 mg/day (158, 12 centers)		Very weak	Suggests that the reported cardiovascular benefits of spironolactone in PD (survival, events, reduced left ventricular mass, reduced hypokalemia) are *not* due to effects on salt and water balance
		Difference in rate of decline urine volume (24 m)	No difference (CI not reported)		
	Lin et al. [71]	Spironolactone, 25 mg (253, 40% on PD)	No difference (CI not reported)		
	Yongsiri et al. [72]	Difference in rate of decline urine volume (24 m)	No difference (CI not reported)		
		Spironolactone, 25 mg (24, cross-over study, 1 m)			
		Difference in urine volume or sodium excretion			

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Table 46.6 Interventions to ameliorate worse outcomes associated with fast solute transfer by influencing salt and water balance (by increasing removal and preventing reabsorption).

Outcomes	Source	No. of participants (no. of studies)	Relative risk or effect (95% CI)	Certainty of evidence	Conclusion
(a) Use of APD versus CAPD					
All-cause mortality	**Brimble et al. meta analysis** [19]	**6648 (19 studies)**	In centers with no APD increased mortality: 1.3 (0.6, 2.7) Meta-regression: Significant interaction showing reduced mortality as proportional use of APD by centers increases ($P = 0.05$)	Low •	Taken together these observational studies, combined with our understanding of peritoneal physiology, suggest that use of APD may mitigate the increased mortality risk associated with rapid peritoneal solute transfer
	ANZDATA Registry [74]	**628 fast transporters** 142 APD 486 CAPD	Multivariate intent-to-treat use of APD: 0.56 (0.35, 0.87) As treated with APD: 0.72 (0.54, 0.96) Case control (APD): 0.6 (0.36, 0.96) Only ever APD versus only ever CAPD: 0.29 (0.14, 0.6)	Moderate ••	
	Davita database [22]	**10 142 (764 centers)** 8874 ever used APD 1268 never used APD	Per 0.01 increase in solute transport 1.06 (0.99, 1.12) ⎫ *significant interaction* 1.15 (0.98, 1.35) ⎭ *($P < 0.05$)*	Moderate ••	
Hospitalization	**Davita database** [22]	As above 8874 ever used APD 1268 never used APD	1.03 (1.02, 1.04) ⎫ *significant interaction* 1.11 (1.05, 1.16) ⎭ *($P < 0.05$)*	Weak ••	APD possibly reduces hospitalization
(b) Use of polyglucose solution (icodextrin)					
Increased Net Ultrafiltration (mL/d)	**Cho et al.** [75]	102 (4)	448.5 ml (289.2, 607.8)	Moderate •••	Icodextrin probably increases net salt and water removal
Uncontrolled fluid overload episodes	**Cho et al.** [75]	100 (2)	0.30 (0.15, 0.59)[a]	Moderate •••	Icodextrin probably reduces uncontrolled fluid overload
Reduced extracellular fluid volume (mL)	**Davies et al.** [76] **Konings et al.** [77]	50 (1) estimated from bioimpedance 32 (1) estimated from NaBr dilution	−1060 ml (−305, −1815) *Comparator glucose 2.27%* −2600 ml (−548, −4652) *Comparator glucose 1.36%*	Moderate •••	Icodextrin probably reduces the extracellular fluid volume

APD, automated peritoneal dialysis; CAPD, continuous ambulatory peritoneal dialysis.
[a] For absolute effects, summary of adverse effects and more detail see Chapter 3, recommendation 2.
Source: Htay et al. [75] and Lambie et al. [23].

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Mitigation of Poor Ultrafiltration Associated with Fast Solute Transport

As outlined above, the problems of poor salt and water balance in the context of fast small solute transfer are twofold: early loss of ultrafiltration in the dwell followed by more rapid reabsorption of salt and water. This problem may be underestimated in CAPD patients if the overfill of dialysis bags is not accounted for in the calculation of daily ultrafiltration (an overestimate of 100–200 ml ultrafiltration per exchange) [73]. There are two tools available to clinicians to solve this problem. One is the use of APD, which allows the dwells to be shortened thereby ensuring net ultrafiltration (and in fast transport patients there will be more rapid diffusion of sodium, so the negative effects of sodium sieving are less of a concern). The other tool is icodextrin, which prevents fluid reabsorption during the long exchange. If APD and polyglucose (icodextrin) are not available, it is still usually possible to construct regimens that obviate excess fluid absorption, even if this requires more dialysate glucose. The evidence supporting these interventions is summarized in Table 46.6, although the chapter on dialysis solutions covers the evidence for polyglucose solutions in more detail, including the benefits not directly related to salt and water balance. Broadly, in observational studies APD is associated with reduced mortality and hospitalization in fast transporters but does not fully abrogate the risk (Table 46.6a) [19, 22, 74]. There are no trials published that address this issue directly (i.e. salt and water removal in APD versus CAPD according to membrane transport characteristics). A Cochrane systematic review found no differences by modality in survival or residual kidney function, but the number and sample sizes of trials were extremely small [78]. Polyglucose does improve salt and water removal [75, 79], in particular by preventing excessive reabsorption [80], which translates into improved fluid status [76, 77] and can reduce the risk of acute episodes of fluid overload (Table 46.6b) [75, 79]. There are no randomized studies powered to interrogate cardiovascular or mortality outcomes. A more detailed discussion and summary of potential adverse effects can be found in Chapter 3.

Conclusion

Achieving salt and water balance to obtain optimal fluid status in PD requires knowledge and integration of a number of components, e.g. clinical and nutritional assessment, blood pressure, membrane function, and body composition. The evidence to support clinical decision-making is limited. Nevertheless, cohort studies have identified key factors, such as fast peritoneal solute transfer, ultrafiltration insufficiency, and worse outcomes associated with low salt and water removal, that must be taken into account. Our improved understanding of membrane (patho-)physiology provides a strong rationale for our recommended treatment interventions, although the evidence certainty remains low due to the lack of hard outcomes reported. This mechanistic understanding does inform clinical practice and should be considered an important evidence source on which to make clinical judgments. There are still considerable evidence gaps to be filled. These include the role for volume assessment technologies in guiding fluid management and the balance between normalizing fluid status, maintaining residual kidney function, and the role of pharmacological agents in achieving optimal clinical outcomes.

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Solutions

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Introduction

Peritoneal dialysis (PD) is a well-established form of kidney replacement therapy (KRT) [1, 2], with possible early survival advantage as compared to hemodialysis [3–5]. Preservation of residual renal function (RRF) is of paramount importance in PD given that RRF contributes significantly to survival advantage in PD patients [6]. Conventional PD solutions are considered bio-incompatible in light of their low pH, high lactate concentrations, and high glucose concentrations with high glucose degradation product (GDP) content, which are generated during the heat sterilization process [7–14]. GDPs cause renal tubular apoptosis [15], which can potentially result in decline of RRF. Studies have reported that low pH in conventional solutions is a culprit for inflow pain in PD patients [16, 17]. More importantly, the bio-incompatible nature of conventional solutions has been reported to have a negative impact on the growth of mesothelial cells [7, 10–14] and the function of phagocytic cells [8]. Chronic exposure to conventional solutions has been implicated in the pathogenesis of peritoneal membrane fibrosis, which stems from loss of mesothelial cells, epithelial-to-mesenchymal transition of mesothelial cells, thickening of the submesothelial compact zone, and development of vasculopathy [18–20].

In this chapter, we summarize the published studies available for neutral pH, low GDP solution, icodextrin, or amino acid-based solutions in the treatment of peritoneal dialysis and provide recommendations for the nephrologist treating patients on peritoneal dialysis (Table 47.1).

Epidemiology

The recent Global Kidney Health Atlas (GKHA) survey reported that chronic PD service was available in only 76% of the countries worldwide, with particularly reduced accessibility in low-income countries (23%) [23]. The majority of PD patients are on conventional PD solutions, although some countries, including India, China, and Latin American countries, practice domestic manufacture of PD solution in order to reduce the cost by avoiding transport fees and import taxes [24]. Neutral pH, low GDP biocompatible solutions are less widely available than conventional solutions, and are primarily restricted to high-income and upper-middle-income countries. Similarly, glucose polymer-icodextrin is also not universally available. The limited access of lower-middle and low-income countries to biocompatible solutions is probably related to funding and healthcare policies given that these solutions are generally more expensive than conventional solutions. The recent GKHA survey reported that PD patients from low-income countries pay a large proportion of dialysis treatment costs using out-of-pocket money [23].

Pathophysiology

In an attempt to overcome the unphysiological nature of conventional solutions, biocompatible solutions were introduced and have been available for almost two decades. Neutral pH and low GDP solutions have been achieved using dual or triple chamber bag designs in which glucose is kept at a lower pH (2.5–3) in a separate chamber away from

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Table 47.1 Peritoneal dialysis solution.

Treatment	Recommendation	Certainty of evidence	Strength of recommendation
Neutral pH low GDP solution	We suggest that neutral pH, low GDP solution can be used to preserve residual renal function and urine volume in peritoneal dialysis patients. These may be used to reduce inflow pain in peritoneal dialysis patients. Peritoneal dialysis patients may reasonably choose not to use neutral pH, low GDP solutions based on low to very low certainty evidence that treatment makes no difference to peritonitis, technique failure, and mortality.	High (residual renal function, urine volume) Low to very low (peritoneal ultrafiltration, small solute transport, inflow pain, peritonitis, technique failure, and mortality)	Weak [21]
Glucose polymer	We suggest that glucose polymer solution can be used to increase daily ultrafiltration and reduce uncontrolled fluid overload in peritoneal dialysis patients. Peritoneal dialysis patients may reasonably choose not to use glucose polymer as treatment makes no difference to hard outcomes, including technique survival and mortality.	Moderate (daily ultrafiltration, uncontrolled fluid overload) Low to very low (residual renal function, urine volume, rash, peritoneal creatinine clearance, peritonitis, technique survival, and mortality)	Weak [21]

GRADE assessment of the certainty of the evidence [22]: High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different* is low. Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different* is moderate. Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different* is high. Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different* is very high. **Substantially different = a large enough difference that it might affect decision-making.*

electrolytes and buffer to prevent or minimize GDP formation during heat sterilization and storage [25].The seal between chambers is broken prior to use, which enables the final product of a neutral pH, low GDP solution [25]. There have been several different types of low GDP solutions, which differ according to the type of buffer employed (lactate and/or bicarbonate). However, the majority of studies of biocompatible solutions have evaluated lactate-buffered solutions [26–32]. A number of studies have been published regarding the role and potential benefit of neutral pH, low GDP solutions on clinical outcomes, including RRF, urine volume, peritoneal membrane function, ultrafiltration, peritonitis risk, inflow pain, technique survival, and patient survival [26–34].

Glucose has been employed as the principal osmotic agent to promote peritoneal ultrafiltration in PD, but may be harmful to the peritoneal membrane [7, 11, 13, 35, 36]. It is also a source of GDPs [37, 38], which in turn promote advanced glycation end-product (AGE) formation in the peritoneal membrane and correlate with membrane fibrosis [37]. To overcome the disadvantage of glucose in conventional solutions, nonglucose agents have been used as an alternative to glucose. One such example is icodextrin, which not only provides the benefit of avoiding peritoneal glucose exposure but also has the advantage of enhancing ultrafiltration through colloidal pressure, which is especially beneficial for patients with high membrane transport characteristics [39], prolonging an osmotic gradient for fluid removal during the entire dwell. There have been a number of studies comparing the clinical outcomes of icodextrin with conventional solutions [39–43]. Amino acids are another nonglucose osmotic agent that have been examined in the peritoneal dialysis setting as a means of sparing glucose, whilst possibly providing nutritional supplementation [44, 45]. However, very few studies have compared the effects of amino-acid-based solutions with conventional solutions on nutritional indices and other clinical outcomes [45–48].

Treatment

Neutral pH, Low GDP Solutions

Residual Renal Function

The potential benefit of biocompatible solutions on RRF has been examined in multiple RCTs since the early 2000s with conflicting results. Some showed improved RRF [27, 29, 30, 32] while others did not show any benefit [31, 33, 34]. These disparities may have at least been partly due to small trial sample sizes, single center designs, short follow-up durations, and suboptimal methodologic quality. One of the large well-conducted studies of biocompatible solutions on RRF reported that biocompatible solutions were associated with better preservation of urine volume and showed a trend toward preserving the RRF, although the result did not reach

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the statistical significance [27]. However, re-analysis of the effect of biocompatible solution on RRF after adjusting for other potential confounders, including baseline renal function, longitudinal trend of blood pressure, longitudinal trend of peritoneal ultrafiltration, and glucose exposure over time, demonstrated that the use of biocompatible solution was significantly associated with better preservation of RRF compared with conventional dialysis solutions [49]. Meta-analysis of studies evaluating biocompatible solutions published in 2014 reported that the benefit of biocompatible solutions on preservation of RRF was apparent with long-term (>1 year) exposure to biocompatible solutions [50]. However, moderate to severe heterogeneity was observed [50]. Subsequent meta-analysis in 2015 with additional two studies identified reported better preservation of RRF with biocompatible fluids that was observed as early as 6 months follow-up duration. This effect extended beyond 1 year follow-up duration [51]. An updated systematic review of biocompatible solutions reported with high certainty of evidence that use of biocompatible solutions was associated with better preservation of RRF (15 randomized controlled trials [RCTs]: 835 participants, relative risk [RR] 0.19, 95% confidence interval [CI] 0.05 to 0.33) at all the time points examined (12 months, 12–24 months, and beyond 24 months) [21] (Table 47.2).

Urine Volume

The association of urine volume and patient survival was first demonstrated by Bargman et al. in a re-analysis of the CANUSA study, in which a 250 ml increase in urine vol-

Table 47.2 Summary of findings: neutral pH, low GDP peritoneal dialysis solutions.

Neutral pH, low GDP PD solutions versus standard glucose PD solutions						
	Anticipated absolute effects (95% CI)					
Outcomes	**Risk with standard glucose dialysate**	**Risk with low GDP dialysate (all buffer types)**	**Relative effect (95% CI)**	**No. of participants (studies)**	**Certainty of the evidence (GRADE)**	**Conclusions**
Residual renal function	The mean residual renal function (GFR) in low GDP group was 0.54 ml/min/1.73 m^2 (0.14–0.93) higher		–	835 (15)	⊕⊕⊕⊕ High	Neutral pH, low GDP solution improves residual renal function
Urine volume	The mean urine volume in low GDP group was 114.37 ml/day (47.09–81.65) higher		–	791 (11)	⊕⊕⊕⊕ High	Neutral pH, low GDP solution improves urine volume
Peritoneal ultrafiltration: 4 h	The estimated mean peritoneal ultrafiltration in low GDP group was 69.72 ml/4 h (16.60–122.84) lower		–	414 (9)	⊕⊕⊖⊖ Low	Neutral pH, low GDP solution may slightly reduce peritoneal ultrafiltration during 4-h peritoneal equilibration test
Peritoneal solute transport rate (4-h dialysate: plasma creatinine)	The mean peritoneal solute transport rate in low GDP group was 0.01 (0–0.03) higher		–	746 (10)	⊕⊕⊖⊖ Low	Neutral pH, low GDP solution may slightly increase peritoneal solute transport
Peritonitis rate (episodes/total patient-months)	31 per 1000	36 per 1000 (26 to 51)	RR 1.18 (0.84–1.64)	18 184 (10)	⊕⊕⊖⊖ LOW	Neutral pH, low GDP solution may make little or no difference to peritonitis rate
Technique failure (death-censored)	74 per 1000	81 per 1000 (55 to 120)	RR 1.10 (0.75–1.63)	1275 (15)	⊕⊕⊖⊖ LOW	It is uncertain whether neutral pH, low GDP solution reduces technique failure
Death (all causes)	77 per 1000	21 per 1000 (41 fewer to 11 more)	RR 0.73 (0.47–1.14)	1229 (15)	⊕⊕⊖⊖ LOW	It is uncertain whether neutral pH, low GDP solution reduces death (all-cause)

CI, confidence interval; RR, risk ratio; GRADE assessment of the certainty of the evidence.
GRADE assessment of the certainty of the evidence [22]: High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different* is low. Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different* is moderate. Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different* is high. Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different* is very high. **Substantially different = a large enough difference that it might affect decision-making.*
Source: Htay et al. [21].

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ume was associated with 36% reduction in risk of mortality [6]. One of the largest multicenter trials examining the effects of biocompatible solutions on RRF reported longer time to anuria and better preservation of residual urine volume with biocompatible solutions than conventional PD solutions [27]. This finding was supported by subsequent meta-analysis of RCTs (seven studies, 520 participants), who reported larger urine volume with the use of biocompatible solutions than conventional solutions [50]. In the latest update review of biocompatible solutions by Htay et al. it was reported with a high certainty of evidence that use of biocompatible solutions improved urine volume, (11 RCTs, 791 participants, RR 0.21, 95% CI 0.05–0.37), which was observed beyond 12 months of follow-up duration (Table 47.2) [21].

Peritoneal Membrane Function

Previous meta-analysis reported no difference in peritoneal ultrafiltration between neutral pH, low GDP, and conventional solutions [50]. A recently updated Cochrane review reported with low certainty evidence that neutral pH, low GDP solutions may slightly reduce peritoneal ultrafiltration during the 4-hour peritoneal equilibration test. It is uncertain whether neutral pH, low GDP solutions reduce 24-hour peritoneal ultrafiltration compared with conventional PD solutions given that considerable statistical heterogeneity was observed [21].

Biocompatible solutions may slightly increase 4-hour dialysate:plasma creatinine ratio in low certainty evidence [21] (Table 47.2). However, a previous study examining the longitudinal trend of membrane solute transport reported lower 4-hour dialysate:plasma creatinine ratio with biocompatible solution [52]. Most studies included in the meta-analysis did not examine the longitudinal changes in peritoneal solute transport but rather reported the solute transport at a single time point at the end of the study [50, 51]. More studies are needed to examine the effect of biocompatible solution on peritoneal membrane transport status.

Peritonitis

Peritonitis is one of the most common reasons for patients discontinuing PD therapy [53, 54]. The first RCT to show the potential effects of biocompatible solutions on the risk and severity of peritonitis was reported in the BalANZ trial, in which patients receiving biocompatible solutions experienced fewer peritonitis episodes than those on conventional solutions, and peritonitis episodes were rated as being milder in severity [27]. It was postulated that bioincompatibility of conventional PD solutions, due to acidic pH and high GDP content, would have adversely impacted on local host defense mechanisms, including impaired phagocytic function of macrophages and polymorphonuclear leukocytes, thereby rendering patients more susceptible to infection [8, 27].

Despite the promising results from the previous large RCT, the findings of benefit of biocompatible solutions on the risk and severity of peritonitis were unable to be replicated in subsequent RCTs [28–30, 32, 33]. Similarly, the benefit of biocompatible solutions on the risk and rate of peritonitis was unable to be demonstrated in a systematic review and meta-analysis [50], although subgroup analysis of studies with a low risk of attrition bias did find an appreciably lower risk of peritonitis with biocompatible solutions compared to conventional PD solutions [21]. Given that a considerable number of studies in the meta-analysis had a high risk of attrition bias (median drop-out 51%), it was concluded from low certainty evidence that neutral pH, low GDP solution may make little or no difference to the risks of peritonitis or peritonitis rates compared with conventional PD solutions (Table 47.2).

Technique Failure and Mortality

Most available studies on biocompatible solutions have been too small with too short a follow-up duration to have adequate statistical power to examine hard clinical outcomes, including technique failure and mortality. It is therefore uncertain whether neutral pH, low GDP solutions reduce technique failure or mortality [21, 50].

Inflow Pain

Inflow pain can significantly affect the quality of life of patients on peritoneal dialysis. Inflow pain has been mainly attributed to the low pH of conventional solution and improvement in the acidity of the solution with neutral pH, low GPD solution has shown decreased the burden of inflow pain [55]. In low certainty evidence, neutral pH, low GDP solutions may slightly improve inflow pain [50].

Adverse Effects

The available data have not demonstrated any harms resulting from the use of neutral pH, low GDP solution compared with conventional PD solution [50].

Bicarbonate ± Lactate Buffered Solution

The majority of studies comparing the clinical outcomes of neutral pH, low GDP solutions versus conventional solutions used neutral pH, low GDP, lactate buffered solutions rather than pure bicarbonate buffered or bicarbonate/lactate buffered solutions. The results of meta-analyses of neutral pH, low GDP solutions have therefore been heavily based

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on the findings of RCTs with low GDP, lactate buffered solutions. For example, in a meta-analysis of neutral pH, low GDP solutions evaluating RRF, 10 out of 15 RCTs used lactate buffered solution, only three RCTs used pure bicarbonate buffered solutions, and two RCTs used a mixture of lactate buffered and bicarbonate/lactate buffered solutions [21].

There were few studies comparing the effects of bicarbonate/lactate buffered or pure bicarbonate buffered solutions with lactate buffered solutions [55–59]. Mactier et al. conducted a double-blind, cross-over RCT comparing the effects of different PD solutions, including bicarbonate buffered, bicarbonate/lactate buffered, and conventional solutions, on inflow pain using a verbal rating scale and the validated McGill Pain Questionnaire in 18 patients. They reported that inflow pain was significantly reduced with both bicarbonate or bicarbonate/lactate buffered solutions compared to conventional solution, and bicarbonate/lactate buffered solution was the most effective in alleviating pain [58].

Another area of interest with respect to the comparative effects of bicarbonate or bicarbonate/lactate buffered solutions and conventional solutions is correction of metabolic acidosis. A previous cross-over RCT including 28 patients (children, age 6 months to 15 years) reported that neutral pH, low GDP, bicarbonate buffered solution achieved more effective correction of metabolic acidosis than conventional lactate buffered solution [56]. A multicenter RCT comparing the effect of bicarbonate/lactate buffered versus conventional lactate buffered solution on correction of acidosis reported that venous plasma bicarbonate level increased by 3.1 mmol/l from a baseline level of 23 mmol/l in patients treated with bicarbonate/lactate buffered solution during the study period, and that the number of patients with acidosis (defined as plasma bicarbonate <24 mmol/l) was significantly reduced in the bicarbonate/lactate group [60]. However, a multicenter RCT comparing bicarbonate/lactate versus lactate buffered solution in 123 patients (only 69 patients completed the 6-month study) was unable to demonstrate any significant difference in acid-base status between the two groups [61]. This finding, however, has to be interpreted with caution given the suboptimal quality of the study and associated high risk of attrition bias.

Glucose Polymer Dialysate (Icodextrin)

Ultrafiltration

Icodextrin is a high molecular weight, iso-osmolar, glucose polymer that was first used in a clinical study in the 1980s [62]. Since then, several studies have been published on the effect of icodextrin on peritoneal ultrafiltration as compared with that of different strengths of conventional solutions, including 1.36%, 2.27%, or 3.86% dextrose solution during the long dwell (over 8–16 hours) either as a day- or night-dwell [39–41, 63, 64]. The updated meta-analysis, including four RCTs (102 participants), reported that icodextrin probably improves peritoneal ultrafiltration in moderate certainty evidence [21, 50] (Table 47.3).

Icodextrin has been demonstrated to generate better ultrafiltration compared with conventional dextrose solutions (1.36% or 2.27%). Patients with high peritoneal membrane solute transport characteristics have been known to experience poor peritoneal ultrafiltration with conventional solutions, especially during the long dwell [65], which is considerably augmented with the use of icodextrin [65, 66]. A meta-analysis of two RCTs (100 participants) reported that icodextrin probably reduces uncontrolled fluid overload (371 fewer per 1000); moderate certainty evidence [21, 50] (Table 47.3).

Technique Survival

A previous RCT conducted by Takatori et al. in 41 patients with diabetes and end-stage kidney disease reported better technique survival with icodextrin (71.4% vs. 45%) [67]. Although there has been evidence that icodextrin improves ultrafiltration and reduces uncontrolled fluid overload, available data from meta-analysis suggests that icodextrin may make little or no difference to technique survival; very low certainty evidence [50] (Table 47.3).

Residual Renal Function

There have been conflicting results regarding the effects of icodextrin on RRF and urine volume. A previous RCT by Konings et al., including 40 patients of whom only 33 (19 on icodextrin and 13 controls) completed the trial, reported a significant decline in RRF (glomerular filtration rate [GFR] 4.8–3.2 ml/min) and urine volume (1131–913 ml) over a 4-month follow-up period in the icodextrin group, which the authors postulated was due to a reduction in overhydration-stimulated pressure diuresis [68]. However, a multicenter RCT conducted by Davies et al. including 50 patients with urine output <750 ml reported that there was no significant reduction in urine volume in the icodextrin group [69]. Meta-analysis, to date, reported that icodextrin may make little or no difference to RRF (four RCTs, 114 participants, RR 0.12, 95% CI −0.26–0.49) and residual urine volume (three RCTs, 69 participants, RR −0.10, 95% CI −0.58–0.38); low certainty evidence [21, 50] (Table 47.3).

Solute Clearance

Apart from improving daily ultrafiltration, icodextrin may make little or no difference to peritoneal creatinine clearance (three RCTs, 237 participants).

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Table 47.3 Summary of findings: glucose polymer (icodextrin).

Glucose polymer (icodextrin) versus standard glucose dialysate for PD						
	Anticipated absolute effects (95% CI)					
Outcomes	**Risk with standard glucose dialysate**	**Risk with glucose polymer (icodextrin)**	**Relative effect (95% CI)**	**No. of participants (studies)**	**Certainty of the evidence (GRADE)**	**Conclusions**
Uncontrolled fluid overload	531 per 1000	159 per 1000 (80–313)	RR 0.30 (0.15–0.59)	100 (2)	⊕⊕⊕⊖ Moderate	Icodextrin probably reduces uncontrolled fluid overload
Rash	43 per 1000	109 per 1000 (26–466)	RR 2.51 (0.59–10.72)	755 (3)	⊕⊕⊖⊖ Low	Icodextrin may slightly increase risk of rash
Residual renal function (renal CrCl)	The mean residual renal function (renal CrCl) in the icodextrin group was 0.30 ml/min higher (0.65 lower to 1.23 higher)		–	114 (4)	⊕⊕⊖⊖ Low	Icodextrin may make little or no difference to residual renal function
Urine volume	The mean urine volume was 88.88 ml/day lower with icodextrin (356.88 lower to 179.12 higher) than standard glucose dialysate		–	69 (3)	⊕⊕⊖⊖ Low	Icodextrin may make little or no difference to urine volume
Daily ultrafiltration	The mean daily ultrafiltration was 448.54 ml/day higher with icodextrin (289.28 to 607.8 higher) than standard glucose dialysate		–	102 (4)	⊕⊕⊕⊖ Moderate	Icodextrin probably improves daily ultrafiltration
Peritonitis	236 per 1000	12 per 1000 (54 fewer to 42 more)	RR 0.95 (0.77–1.18)	667 (6)	⊕⊕⊖⊖ Low	Icodextrin may make little or no difference to peritonitis risk
Technique failure (death-censored)	107 per 1000	64 per 1000 (34 to 120)	RR 0.60 (0.32–1.12)	350 (4)	⊕⊖⊖⊖ Very low	Icodextrin may make little or no difference to technique failure

CI, confidence interval; RR, risk ratio; GRADE assessment of the certainty of the evidence.
GRADE assessment of the certainty of the evidence [22]: High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different* is low. Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different* is moderate. Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different* is high. Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different* is very high. **Substantially different = a large enough difference that it might affect decision-making*.
Source: Htay et al. [21].

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Table 47.4 Comparison of contents of different peritoneal dialysis solutions.

Components	Conventional solution	Low GDP solutions					
		Balance	Physioneal	Gambrosol trio	Bicavera	Extraneal	Nutrineal
Osmotic agent	Glucose	Glucose	Glucose	Glucose	Glucose	Icodextrin	Amino acids
(%)	1.5/2.5/4.25	1.5/2.5/4.25	1.5/2.5/4.25	1.5/2.5/4.25	1.5/2.5/4.25	7.5	1.1
Osmolarity (mOsmol/l)	345–483	356–511	344–483	357–483	359–511	284	365
pH	5.5	7.0	7.0–7.4	5.5–6.5	7.4	5.5–6.0	6.7
Lactate (mmol/l)	35–40	35	10–15	0	0	40	40
Bicarbonate (mmol/l)	0	0	25	39–41	34	0	0
Sodium (mmol/l)	132–134	134	132–134	131–133	134	132	132
Chloride (mmol/l)	95–102	100–101.5	95–101	96	104.5	96	105
Calcium (mmol/l)	1.25/1.75	1.25/1.75	1.25/1.75	1.7–1.79	1.75	1.75	1.25
Magnesium (mmol/l)	0.25/0.5	0.5	0.25	0.25	0.5	0.25	0.25
Formaldehyde (μmol/l)[a]	6.8 ± 0.2	<3.3	3.4 ± 0	<3.3	<3.3	3.6 ± 0.7	Not tested
3-DG (μmol/l)[a]	167 ± 0.3	17.6 ± 0.3	93.3 ± 5.0	20.2 ± 2.4	16.3 ± 0.2	7.5 ± 0.4	< 0.1
3,4-DGE (μmol/l)[a]	11.3 ± 0.5	<2.4	14.3 ± 2.5	<2.4	<2.4	<2.4	Not tested

DG, deoxyglucosone; 3,4-DGE, di-deoxyglucosone-3-ene; GDP, glucose degradation products.
[a] Adapted from Jörres [77].

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Peritonitis

Similarly, with moderate certainty evidence, icodextrin probably makes little or no difference to the risk of developing peritonitis. Most of the available RCTs on icodextrin had short follow-up periods, which might not have allowed sufficient time to confidently detect an impact on mortality. It is therefore uncertain whether icodextrin reduces all-cause mortality in PD patients; low certainty evidence [21, 50] (Table 47.3).

Metabolic Parameters

Icodextrin has also been demonstrated in RCTs to improve patients' metabolic profiles. A multicenter RCT conducted by Paniagua et al. including 59 patients followed up for 1-year duration reported that icodextrin use was associated with a better metabolic profile including less glucose absorption, reduced insulin requirement, improved fasting glucose level, reduced HbA1c level, and also lower triglyceride level in diabetic PD patients compared with use of conventional PD solution [66].

Adverse Events

There were few reports about icodextrin use and the development of skin rash [70–72]. In a meta-analysis including three RCTs and 755 participants, icodextrin may have slightly increased the risk of developing rash (66 more per 1000) as compared with conventional solutions; low certainty evidence [21]. In addition, caution should be exercised when monitoring blood glucose levels in diabetes patients who use icodextrin in light of the fact that maltose, which is a metabolite of icodextrin, can be interpreted falsely as glucose, leading to overestimation of blood glucose level by glucose dehydrogenase-based methods using pyrroloquinoline quinone (GDH-PQQ) as a cofactor [73, 74].

Amino Acid Dialysate

Malnutrition is common in PD patients [75] and is a known risk factor for mortality [76]. Peritoneal dialysis itself has been a known cause for loss of amino acids (3–4 g/day) and protein (8–15 g/day) during dialysis exchanges [76]. Supplementing these losses by the use of amino acids as an alternative osmotic agent to dextrose in PD solutions was started in the late 1960s [44] (Table 47.4).

The potential benefit of amino-acid-based solution has been examined in a few studies, but most available studies have been non-RCTs with small sample sizes and/or insufficient follow-up duration to detect hard clinical outcomes, including technique failure and mortality [45, 47, 48]. The largest RCT of amino acid PD solution with the longest follow-up to date was that by Li et al., which included 60 Chinese malnourished patients who were randomized to receive once-daily amino acid solution (nutrineal) or conventional solution and followed up for 3 years [46]. The investigators reported that there were no significant differences observed in composite nutritional indices, technique failure, hospitalization or mortality between the two groups [46]. Based on the available data, it is uncertain whether once-daily amino acid solution improves nutritional parameters in malnourished PD patients.

Conclusions

To date, the available evidence suggests that neutral pH, low GDP PD solutions improve RRF and urine volume and may slightly improve infusion pain compared with conventional PD solutions. However, neutral pH, low GDP solutions may slightly increase peritoneal solute transport and slightly reduce peritoneal ultrafiltration, as measured during a 4-hour peritoneal equilibration test, and may make little or no difference to peritonitis rate. It is uncertain whether neutral pH, low GDP PD solutions improve technique or patient survival. Use of icodextrin probably improves daily ultrafiltration and reduces uncontrolled fluid overload but may make little or no difference to RRF, urine volume, peritoneal creatinine clearance, and technique or patient survival. Icodextrin may slightly increase the risk of rash. It is uncertain whether once-daily amino acid solution improves nutritional indices in malnourished patients. Future large well-conducted studies with sufficient follow-up duration examining the effects of long-term use of neutral pH, low GDP PD solutions on hard clinical outcomes, including technique and patient survival, are needed.

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Peritoneal Dialysis: Infections

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Introduction

Peritoneal dialysis (PD) is a well-established form of renal replacement therapy for patients with end-stage kidney disease (ESKD), which accounts for 11% of dialysis therapy for patients with ESKD worldwide [1].

One of the known complications of PD is infection, in particular PD-related peritonitis, which increases patient morbidity, including hospitalization, loss of catheter, and change of dialysis modality and death. Exit site or tunnel infection can progress to peritonitis. Most PD peritonitis episodes resolve with antimicrobial therapy, although this increases risks of further peritonitis, ultrafiltration failure (UFF) [2], and encapsulating sclerosing peritonitis [2, 3].

PD catheter-related infections are a major predisposing factor to PD-related peritonitis [4]. Implementation of effective prevention measures is the ultimate goal. However, peritonitis continues to represent a significant complication of PD despite the introduction of effective prevention strategies, such as modifications of the PD catheter and connection systems [5]. The primary objective of preventing and treating catheter-related infections is to prevent peritonitis. Treatment is aimed at reducing morbidity and recurrence of peritonitis.

Antimicrobial prophylaxis includes oral and topical antibiotics [6], topical disinfectants, co-prescribed antifungal therapy, and prophylactic treatment of *Staphylococcus aureus* nasal carriage. All of these strategies, particularly cleansing and disinfection of the exit site, are widely accepted, but practice patterns are variable and trial results are conflicting [7–9]. Catheter-related intervention strategies which have been studied include modifications of catheter design, implantation technique, connection methodology, and PD modality [10].

When infection does occur, early and effective management is important to reduce complications, such as progression from exit site infection (ESI) to peritonitis, relapse of peritonitis, hospitalization, catheter removal, hemodialysis transfer, and death. The mainstay of management of peritonitis is antimicrobial therapy, although adjunctive treatments such as use of fibrinolytic agents [11–13], peritoneal lavage, and intraperitoneal immunoglobulin administration [14] have been used. Peritonitis treatment regimens vary with regards to antimicrobial agent(s), route of administration, dosing frequency, and total duration of therapy. Center-specific factors such as patterns of antimicrobial resistance and regional isolation also play a role in making treatment decisions [15]. Each PD unit should examine its own pattern of infection, causative organisms, and sensitivities and adapt the protocols according to local conditions as necessary [16].

This chapter reviews and discusses the evidence for supporting practices in the prevention and treatment of PD-related infections, particularly focusing on peritonitis.

Definition

Standardization definitions for exit site/tunnel infections and peritonitis enables comparison of epidemiology, risks factors, and outcomes of PD-related infections. The International

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Society for Peritoneal Dialysis (ISPD) has published definitions for PD-related infection in its guidelines/recommendation [4, 16]. Rates of infection should preferentially be reported as episodes per patient-year [4, 16].

Exit Site and Tunnel Infections

An ESI is defined as the presence of purulent drainage from the exit site. This may or may not be accompanied by peri-catheter swelling or erythema of the skin at the catheter-epidermal interface [4, 16]. Erythema or serous discharge alone may or may not represent infection. A positive culture from a swab in the absence of clinical signs may represent bacterial colonization not infection.

Tunnel infection in the absence of concomitant ESI is rare. Tunnel infection is defined as the presence of signs of inflammation (erythema, edema, and/or tenderness) or ultrasonographic evidence of collection along the subcutaneous catheter tunnel [4, 16].

Peritonitis

Peritonitis can be directly related to the PD procedure (PD-associated peritonitis) or can be surgical peritonitis related to intra-abdominal events, such as perforated viscera. This chapter will focus on the prevention and treatment of PD-associated peritonitis.

General definitions of different types of peritonitis are listed here – diagnosis of peritonitis will be discussed further later in the chapter:

Refractory peritonitis – failure of the PD effluent to clear after 5 days of appropriate antibiotics [16].

Relapsing peritonitis – an episode that occurs within 4 weeks of completion of therapy for a prior episode with the same organism or one sterile episode [16].

Repeat peritonitis – an episode that occurs more than 4 weeks after completion of therapy for a prior episode with the same organism [16].

Recurrent peritonitis – an episode that occurs within 4 weeks of completion of therapy for a prior episode but with a different organism [16].

Epidemiology

The incidence of ESI has reduced since the use of prophylactic topical antimicrobial agents as standard of care [6, 17–20]. Similarly, the incidence of peritonitis has improved with the introduction of disconnect systems [21, 22]. The peritonitis rate has been reported to have reduced from 1.1 to 0.46 episodes per patient year from 1994 to 2003 in a single center study from Hong Kong [21]. This improvement was in parallel with replacement of spike PD sets with a disconnect system which resulted in reduction of peritonitis due to Gram-positive organisms [21].

Risk factors for developing peritonitis include advancing age, some ethnicities (particularly Indigenous and First Nations peoples), comorbidities such as diabetes mellitus and obesity, tropical/temperate climates, depression, nasal carriage of *S. aureus*, and the presence of an ESI [23]. Catheter design and implantation technique and connection methodology also modulate the risk of peritonitis. In addition, some studies have shown that PD modality (continuous ambulatory peritoneal dialysis [CAPD] or automated peritoneal dialysis [APD]) affects peritonitis rates [24–26], although other studies have not confirmed this [27, 28].

PD-associated peritonitis results in significant morbidity and mortality. Catheter removal becomes necessary in cases not responding to antibiotic therapy. This may be temporary and followed by a return to PD, or permanent, resulting in technique failure. UFF can occur both acutely due to increases in capillary permeability and in the longer term resulting in technique failure.

In many countries, peritonitis is a leading cause of permanent transfer to hemodialysis. Peritonitis is prevalent among patients with encapsulating sclerosing peritonitis and may be a causal factor [29]. It is estimated that PD-associated peritonitis results in death in approximately 6–10% of affected patients [30, 31].

Pathophysiology

Catheter exit sites can be colonized with bacteria shortly after catheter placement. Biofilm formation following colonization of bacteria can promote bacterial growth and protect them from topical antimicrobial agents [32, 33]. Colonization can lead to ESI, especially following exit site trauma. Infection can either be localized to the exit site only or can extend to involve the tunnel tract leading to a tunnel infection or even further leading to peritonitis [34, 35]. Severity of infection usually depends on the virulence of the causative organisms. Common causative organisms for ESI are Gram-positive organisms, including Staphylococcus species especially coagulase negative *Staphylococcus*. Common Gram-negative organisms causing ESI include *Escherichia coli* and *Pseudomonas aeruginosa* [36].

The most common serious complication of PD is infection of the peritoneal lining – peritonitis. PD patients can acquire peritonitis through different mechanisms, in which microorganisms can gain access to the peritoneum through

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touch contamination during the dialysis exchange, translocation from the bowel, hematogenous dissemination, or from exit site/tunnel infection.

Diagnosis

Diagnosis of Exit Site and Tunnel Infections

ESI is diagnosed by the presence of purulent drainage from the exit site, with or without erythema of the skin at the catheter-epidermal interface or peri-catheter swelling [4, 16].

Peri-catheter erythema without purulent drainage is sometimes an early indication of infection but can also be a simple skin reaction, particularly in a recently placed catheter or after trauma to the catheter. A positive culture from a swab in the absence of clinical signs may represent bacterial colonization not infection.

Tunnel infection may present as erythema, edema, or tenderness over the subcutaneous pathway but is often clinically occult. A tunnel infection usually occurs in the presence of an ESI but rarely occurs alone. Ultrasound assists in establishing the presence of fluid collection along the subcutaneous catheter tunnel.

Diagnosis of Peritonitis

Diagnosis of peritonitis must be confirmed by the presence of two out of three of the following findings [16]:

1) abdominal pain or cloudy effluent
2) effluent fluid with leukocyte count over 100 cells per microliter (after a dwell time of at least 2 hours), with more than 50% neutrophils
3) positive culture of peritoneal effluent.

The patient experiencing infectious peritonitis often satisfies all the above criteria. However, not all centers can perform a Gram stain, and the culture becomes positive many hours and sometimes days after admission. Decision on treatment is therefore often based on the first two findings. The diagnostic workup is contributed to by the clinical history, fever occurrence, increased peripheral blood leukocyte count, and other typical symptoms of infectious diseases.

1) Cloudy effluent
   This sign must be confirmed by differential count of white blood cells in the peritoneal effluent; a percentage of neutrophils greater than 50% are as important as a total white cell count of 100 cells per microliter. The increase in white cell count can be delayed in some cases; therefore, a white blood cell count lower than 100 per microliter does not rule out the diagnosis of peritonitis, such that accompanying signs and symptoms should be considered. A repeat count on the effluent following an exchange often shows a cell count increase. Leukocyte esterase reagent strips are used in many centers to enable the patient to check the effluent at home thereby reducing the time to diagnosis and avoiding underestimation of the significance of mild changes in effluent clearness. The sensitivity and specificity of the leukocyte esterase test is comparable to that of visual assessment and light microscopy.
   A cloudy peritoneal effluent can also appear in other conditions besides infectious peritonitis such as mild hemoperitoneum, peritoneal eosinophilia, chylous effluent, chemical peritonitis, and peritoneal-based malignancy.
   A cloudy fluid can often appear in the first bag exchange after a period of empty abdomen ("dry abdomen") and is due to the accumulation of cells in the peritoneal cavity. This may lead to the misdiagnosis of peritonitis in patients undergoing intermittent PD or APD with a dry day, as the first exchange is often cloudy in these patients. This can be avoided by infusing 1 l of PD fluid and allowing it to dwell for a minimum of 1–2 hours before draining and examining for turbidity and for cell count; otherwise, a rapid flushing of the peritoneal cavity with 1–2 l of dialysis fluid can precede that maneuver. Clear effluent is typically observed when dialysis fluid is constantly present and regularly exchanged in the peritoneal cavity.
2) Abdominal pain
   In peritonitis, abdominal pain is typically generalized and is often associated with rebound tenderness. Pain in PD-related infectious peritonitis is often first located in the epigastric region; pain then spreads to the entire abdomen. The intensity of pain is variable; some patients have a frank cloudy effluent with little pain, others complain of severe pain which is not necessarily correlated with changes in the cloudiness of the effluent. The causative microorganism could play a role in the severity of pain, for example streptococcal peritonitis is generally associated with severe pain.
   Peritonitis in PD patients may be secondary to disease of abdominal organs. The differential diagnosis between PD-related peritonitis and peritonitis secondary to other diseases is critical for both diagnostic workup and treatment. Pain localized to the left iliac fossa should be suspicious for diverticulitis; first localized pain in the right iliac fossa necessitates evaluation for appendicitis. Consider cholecystitis when pain is in the right hypochondrium.

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3) Positive culture of peritoneal effluent

Gram stain is only positive in a minority of cases, but it is recommended as it may provide a rapid indication of fungal peritonitis.

A positive culture typically occurs in 80–90% of peritonitis episodes. Causative microorganisms include Gram negative and Gram positive bacteria, fungi, yeasts, typical, and atypical mycobacteria. The possibility of a viral peritonitis cannot be excluded, but the literature on this topic is only anecdotal.

PD effluents cultures are negative in 10–20% of cases of clinically diagnosed infectious peritonitis. The low concentration of microorganisms in the effluent accounts for negative culture results but other causes have been reported, above all insufficient volume of the effluent sample, concurrent use of antibiotics, inadequate culture technique or lack of concentration by centrifugation. Other causes are endotoxins or either contaminants of the dialysis fluid or medications introduced in the peritoneal cavity. The ISPD Guidelines suggest that suggest that sampling and culture methods be reviewed and improved if more than 15% of peritonitis episodes are culture-negative [16].

Other signs/symptoms or significant investigation results may also be present in peritonitis, including pneumoperitoneum, elevate amylase concentration in peritoneal fluid, exit site or tunnel infection, leukocytosis, fever, and anorexia. Other important clinical signs and symptoms, including chills, vomiting, lack of bowel sounds, tachycardia, hypotension, and polypnoea, occur in the most severe cases. In some patients (e.g. elderly or on immunosuppressive therapy), these signs can be less severe.

Prognosis

The prognosis of PD-related infection depends on patient and treating center characteristics [37]. One of the patient-level characteristics reported to be responsible for outcomes of peritonitis is causative microorganisms [37]. A previous study including 3305 episodes of peritonitis by Cho et al. reported that some micro-organisms (*Coagulase-negative Staphylococci*, *Streptococci*, and culture negative) were associated with a low risk (<20%) of catheter removal, other microorganisms (including *Corynebacteria*, *Enterococci*, *S. aureus*, and nonpseudomonas Gram-negative organisms) were associated with a moderate risk (20–40%) of catheter removal, and polymicrobial, fungal, and *Pseudomonas* organisms were associated with a high risk (>40%) of catheter removal [38].

Center-level characteristics that have been reported to be associated with more favorable peritonitis outcomes include maintaining a higher proportion of dialysis patients on PD and having a higher percentage of peritonitis episodes treated with empiric antibiotics covering both Gram-positive and Gram-negative organisms at initial presentation [37].

The majority of patients who develop peritonitis achieve cure with antibiotic therapy [37]. The other possible outcomes of peritonitis include catheter removal, transfer to hemodialysis, relapsing or recurrent peritonitis, or death. In a study of a registry data including 9100 episodes of peritonitis, Htay et al. reported that 69% of peritonitis episodes achieved cure with antibiotics therapy [37]. Episodes of peritonitis which did not response to medical therapy developed one or more of the following: catheter removal (19%), transfer to hemodialysis (18%), relapsing or recurrent peritonitis (12%), and mortality (9%) [37].

Prevention

Prevention of PD-related infection plays a critical role in PD as most PD-related infections are preventable. Moreover, peritonitis was reported to be independently associated with an increased risk of all-cause mortality, cardiovascular mortality, and infection-related mortality (Table 48.1) [46].

Topical Antimicrobial Agents

In a meta-analysis of mupirocin, including 14 studies examining nasal or topical at catheter exit site versus no treatment, it was reported that mupirocin was effective in prevention of ESI and peritonitis due to *S. aureus* and other organisms [42]. The meta-analysis only included three randomized controlled trials (RCTs) and these three trials examined nasal mupirocin versus no treatment. In the latest Cochrane meta-analysis, which included only three RCTs, it was reported that, in low certainty evidence, nasal antibiotic prophylaxis had uncertain effects on the prevention of peritonitis or exit site/tunnel infection compared with placebo or no treatment [43] (Table 48.2). There was one trial reporting that nasal mupirocin compared with placebo significantly reduced *S. aureus* ESI rate in CAPD patients who were identified as *S. aureus* nasal carriers, but had no significant effect on peritonitis rates [36].

There are very few RCTs examining the effectiveness of topical mupirocin at the catheter exit site in PD patients [47] and most published studies examined those with nasal colonization by *S. aureus*. The greatest concern regarding routine use of topical mupirocin is the risk of emergence of mupirocin-resistant bacteria, which should be monitored closely. The alternative topical antibacterial agents, including gentamicin [48] and medical honey [49], have been examined in RCTs.

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Table 48.1 Prevention and treatment of PD-related infection.

Treatment	Recommendation	Certainty of evidence	Strength of recommendation
Prevention of PD-related infection			
Technique of catheter insertion	We do not suggest any specific method of catheter insertion	*Low or moderate* (peritonitis) *Very low or low* (exit site infection, technique failure and all-cause mortality)	Weak [39, 40]
Type of catheter	We do not suggest any specific type of catheter be used to prevent PD-related infections	*Low or moderate* (peritonitis and exit site infection) *Very low or low* (technique failure and all-cause mortality)	Weak [39, 40]
PD sets and connection methods	We recommend that Y-set or double bag systems be used to reduce the risk of PD-related peritonitis compared with spike systems	*Moderate or high* (risk of peritonitis and peritonitis rate)	Strong [41]
Prophylactic topical antibiotics at exit site	We suggest that topical antibiotics at exit site may be used to reduce exit site/tunnel infection and peritonitis	*Low* (peritonitis and exit site/tunnel infection)	Weak [42]
Prophylactic IV antibiotics prior to catheter insertion	We suggest that prophylactic IV antibiotics prior to catheter insertion may be used to reduce the risk of early PD peritonitis	*Low* (early peritonitis) *Very low* (exit site/tunnel infection)	Weak [43]
Topical disinfectants	We do not suggest any specific type of topical disinfectant be applied to the exit site to prevent peritonitis, exit site/tunnel infection, or catheter removal/replacement	*Low* (peritonitis, exit site/tunnel infection and catheter removal/replacement)	Weak [43]
Nasal antibiotics	We suggest that PD patients may reasonably choose not to use nasal antibiotics to prevent peritonitis, exit site/tunnel infection, or catheter removal/replacement	*Low* (peritonitis, exit site/tunnel infection and catheter removal/replacement)	Weak [43]
Antifungal prophylaxis	We suggest that antifungal prophylaxis may be used to prevent fungal peritonitis during any course of antibiotics prescribed in PD patients	*Low* (fungal peritonitis)	Weak [43]
Treatment of PD-related infection			
Glycopeptides-based regimen for peritonitis	We suggest that a glycopeptide-based regimen may be used to treat peritonitis in PD patients. PD patients with peritonitis may reasonably choose to receive an alternative nonglycopeptide-based antibiotic regimen to prevent primary treatment failure, relapse, and catheter removal	*Low* (complete cure) *Very low* (primary treatment failure, relapse peritonitis, and catheter removal)	Weak [44]
IP route of administration of antibiotics during peritonitis	We suggest that IP antibiotics may be used to treat peritonitis in PD to increase complete cure and reduce primary treatment failure	*Low to very low* (primary treatment failure, complete cure, and relapse peritonitis)	Weak [44]
Intermittent dosing regimen	We suggest that either an intermittent or continuous dosing IP antibiotic regimen may be used to treat peritonitis in PD patients	*Low to very low* (complete cure and primary treatment failure)	Weak [44]
Peritoneal lavage	We suggest that PD patients who developed peritonitis may reasonably choose not to receive peritoneal lavage to reduce the likelihood of complete cure, relapse or technique failure	*Very low* (complete cure, relapse peritonitis, and technique failure)	Weak [44]
Urokinase	We suggest that simultaneous catheter removal and replacement be considered to reduce recurrent peritonitis compared with urokinase therapy in patients with recurrent peritonitis	*Low* (recurrent peritonitis)	Weak [44]

IP, intraperitoneal; IV, intravenous; PD, peritoneal dialysis.
GRADE assessment of the certainty of the evidence [45]: High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different* is low. Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different* is moderate. Low:; This research provides some indication of the likely effect. However, the likelihood that it will be substantially different* is high. Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different* is very high. **Substantially different = a large enough difference that it might affect decision-making*.

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Table 48.2 Nasal antibiotics versus no treatment for preventing peritonitis in PD patients.

Outcomes	Relative effect (95% CI)	Absolute effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Conclusions
Peritonitis	RR 0.94 (0.67–1.31)	18 fewer per 1000 (from 91 more to 97 fewer)	338 (three studies)	⊕⊕⊖⊖ Low	Nasal antibiotics make little or no difference to peritonitis
Exit site/tunnel infection	RR 1.34 (0.62–2.87)	56 more per 1000 (from 63 fewer to 308 more)	338 (three studies)	⊕⊕⊖⊖ Low	Nasal antibiotics make little or no difference to exit site/tunnel infection
Catheter removal or replacement	RR 0.92 (0.48–1.78)	Eight fewer per 1000 (from 53 fewer to 80 more)	289 (two studies)	⊕⊕⊖⊖ Low	Nasal antibiotics make little or no difference to catheter removal or replacement

CI, confidence interval; PD, peritoneal dialysis; RR, risk ratio.
Source: Campbell et al. [43].

In a randomized controlled double blinded trial, topical gentamicin reduced catheter infections, time to first catheter infection, and catheter infections due to *P. aeruginosa* compared to mupirocin. Peritonitis rates were not statistically significant on intention to treat analysis (0.56/year compared to 0.30/year for mupirocin and gentamicin groups, respectively,P=0.08) [48]. There were no reports of gentamicin ototoxicity. In a meta-analysis including two trials and 214 participants, topical gentamicin compared to mupirocin had uncertain effects on the prevention of peritonitis (relative risk [RR] 1.39, 95% confidence interval [CI] 0.93–2.07) or exit site/tunnel infection (RR 1.19, 95% CI 0.41–3.46) in PD patients [43].

Another RCT examined topical honey at the catheter exit site versus intranasal mupirocin prophylaxis (only in *S. aureus* carriers) in 371 PD patients [49]. PD-related infection-free survival was not significantly different between the two groups. However, in subgroup analysis, topical medical honey was associated with higher risk of PD-related infection in diabetes patients [49].

Similarly, in a multicenter, double-blind RCT there was no difference for topical mupirocin compared to polysporin triple ointments in the time to first episode of PD-related infection, defined as composite of exit site/tunnel or peritonitis [50].

In a Cochrane meta-analysis comparing topical antimicrobial agents versus placebo or no treatment in PD patients, there was very low certainty evidence for prophylactic oral antibiotics (including ofloxacin, cefalexin, rifampin, or cotrimoxazole) and topical antibiotics (including nasal or exit site mupirocin ointment) on peritonitis, peritonitis rate, exit site/tunnel infection, and exit site/tunnel infection rates compared with placebo or no treatment [43] (Table 48.3). Similarly, in very low certainty evidence, topical antibiotic prophylaxis with either sodium fusidate at the exit site and nasal region or mupirocin at the exit site had uncertain effects on the risks of peritonitis and exit site/tunnel infection compared with oral antibiotics (including ofloxacin or rifampicin) or topical gentamicin cream at the exit site [43].

Topical Disinfectants/Antiseptic Agents

Topical disinfectants have been routinely used to clean the catheter exit site to reduce colonization around the catheter exit site in PD patients. The most commonly used disinfectant examined in the studies was povidone-iodine. In a Cochrane meta-analysis, topical disinfectant at the exit site had uncertain effects on the risks of peritonitis and exit site/tunnel infection compared with standard care or other active treatment, including antibiotics or other disinfectants such as hydrogen peroxide, sodium hypochlorite or chlorhexidine [43] (Table 48.4).

Intravenous Antibiotic Prophylaxis Prior to Catheter Insertion

The latest Cochrane meta-analysis reported in low certainty evidence that prophylactic antibiotics administered prior to PD catheter insertion may reduce the risk of early peritonitis, defined as development of peritonitis within 1 month of catheter insertion, but has uncertain effects on risk of exit site/tunnel infection as compared with no treatment [43]. However, there was no difference in the risk of peritonitis or exit site/tunnel infection more than 1 month after catheter insertion between the interventions [43].

The ISPD guidelines recommend systemic prophylactic antibiotics be administered immediately prior to catheter insertion [4, 16]. The KHA-CARI guidelines recommend use of a first-generation cephalosporin for this purpose based on extrapolations from the results of pre-operative antibiotic trials in patients without ESKD. However, the evidence supporting the use of a first-generation cephalosporin

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Table 48.3 Oral or topical antibiotics versus placebo/no treatment for preventing peritonitis in PD patients.

Outcomes	Relative effect (95% CI)	Absolute effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Conclusions
Peritonitis	RR 0.82 (0.57–1.19)	65 fewer per 1000 (from 68 more to 155 fewer)	395 (five studies)	⊕⊕⊖⊖ Low	Oral, topical or intra-peritoneal antibiotics may slightly improve peritonitis
Exit site/tunnel infection	RR 0.45 (0.19–1.04)	97 fewer per 1000 (from 7 more to 143 fewer)	191 (three studies)	⊕⊕⊖⊖ Low	Oral, topical or intra-peritoneal antibiotics may improve exit site/tunnel infection
Catheter removal or replacement	RR 0.82 (0.46–1.46)	21 fewer per 1000 (from 53 more to 62 fewer)	395 (five studies)	⊕⊕⊖⊖ Low	Oral, topical, or intra-peritoneal antibiotics make little or no difference to catheter removal/replacement

CI, confidence interval; PD, peritoneal dialysis; RR, risk ratio.
Source: Campbell et al. [43].

Table 48.4 Topical disinfectants versus standard care or other treatment (disinfectant or antibiotic) for preventing peritonitis in PD patients.

Outcomes	Relative effect (95% CI)	Absolute effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Conclusions
Peritonitis	RR 0.83 (0.65–1.06)	40 fewer per 1000 (from 14 more to 82 fewer)	853 (six studies)	⊕⊕⊖⊖ Low	Topical disinfectants make little or no difference to peritonitis compared with standard care or other treatment
Exit site/tunnel infection	RR 1.00 (0.75–1.33)	Zero fewer per 1000 (from 57 fewer to 75 more)	973 (eight studies)	⊕⊕⊖⊖ Low	Topical disinfectants make little or no difference to exit site/tunnel infection compared with standard care or other treatment
Catheter removal or replacement	RR 0.89 (0.57–1.38)	10 fewer per 1000 (from 34 more to 39 fewer)	792 (six studies)	⊕⊕⊖⊖ Low	Topical disinfectants make little or no difference to catheter removal or replacement compared with standard care or other treatment

CI, confidence interval; PD, peritoneal dialysis; RR, risk ratio.
Source: Campbell et al. [43].

in PD patients undergoing PD catheter insertion is scant. Recommendation of a first-generation cephalosporin in preference to vancomycin may be a reasonable compromise because of the risk of vancomycin-resistant enterococcus (VRE) and *S. aureus*. The ISPD guidelines address this issue by recommending that each program weigh up the benefits of vancomycin with the risk of emergence of resistant microorganisms.

Prophylactic Antibiotics Prior to Other Procedures

Invasive procedures pose a risk for developing peritonitis. Therefore, a role for antibiotic prophylaxis prior to invasive procedures appears plausible. To date, there has been no randomized trial to support this practice. However, it is recommended by the ISPD to consider prophylactic antibiotics prior to procedures, including dental procedures, cholecystectomy, colonoscopy, polypectomy, and hysteroscopy, based on the findings of observational studies [16].

Prophylactic Antifungal Therapy

Fungal peritonitis has high morbidity (including technique failure) and mortality. Fungal peritonitis is usually preceded by bacterial peritonitis [51]. Prolonged exposure to antibiotics can predispose to secondary fungal peritonitis in PD patients [52]. Few studies examined the effect of prophylactic antifungal therapy, either nystatin or fluconazole, which was given along with antibiotics therapy for peritonitis or other sources of infection [53–59]. The meta-analysis, including two studies and 817 participants, reported in low certainty evidence that antifungal therapy

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may reduce fungal peritonitis [60, 61] (Table 48.5). ISPD and KHA-CARI recommend prophylactic use of nystatin during the course of antibiotic therapy to reduce the incidence of fungal peritonitis [16].

Other Interventions

Trials of UV germicidal chambers around the connection device and antistaphylococcal vaccine also showed no effect of these interventions [43]. There are no controlled trials evaluating the effects of antibacterial soap.

Catheter-related Interventions

There were several RCTs that examined the effects of various catheter-related interventions to reduce the risks of PD-associated infection in PD patients [62–68]. Catheter-related interventions included in systematic reviews are surgical approaches (laparoscopy versus laparotomy, standard insertion and resting versus implantation and subcutaneous burying, midline compared to lateral insertion, etc.), type of PD catheter (straight versus coiled, single versus double cuffed, double versus triple cuffed, antibiotic impregnated versus standard catheters), use of silver rings, and immobilization devices. None of these have been shown to significantly affect the rates of exit site/tunnel infections or peritonitis (Tables 48.6–48.9) [40].

The only catheter-related measure that has been shown to influence infection rate in a systematic review is the use of disconnect systems rather than conventional spike systems [41]. Y-set compared to standard spike systems reduce risk of peritonitis and peritonitis rates, but not rates of exit-site/tunnel infection, catheter removal/replacement, and all-cause mortality [41].

Table 48.5 Antifungal agents versus placebo or no treatment for preventing fungal peritonitis in PD patients.

Outcomes	Relative effect (95% CI)	Absolute effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Conclusions
Fungal peritonitis	RR 0.28 (0.12–0.63)	18 per 1000 (8–40)	817 (two studies)	⊕⊕⊖⊖ Low	Antifungal agents may reduce fungal peritonitis compared with placebo or no treatment

CI, confidence interval; PD, peritoneal dialysis; RR, risk ratio.
Sources: Restrepo et al. [60] and Lo et al. [61].

Table 48.6 Laparoscopy compared to laparotomy for preventing peritonitis in PD patients.

Outcomes	Relative effect (95% CI)	Absolute effect (95% CI)	No. of participants/ patient-months (studies)	Certainty of the evidence (GRADE)	Conclusions
Peritonitis	RR 0.90 (0.59–1.35)	24 fewer per 1000 (99 fewer to 85 more)	315 (four RCTs)	⊕⊕⊕⊖ Moderate	Laparoscopy compared with laparotomy probably makes little or no difference to risk of peritonitis
Peritonitis rate (patient-months)	RR 0.89 (0.39–2.07)	Six fewer per 1000 (from 36 fewer to 63 more)	375 (one RCT)	⊕⊖⊖⊖ Very low	Laparoscopy compared with laparotomy has uncertain effect on peritonitis rate
Exit site/tunnel infection	RR 0.75 (0.21–2.72)	Zero fewer per 1000 (71 fewer to 164 more)	270 (three RCTs)	⊕⊕⊖⊖ Low	Laparoscopy compared with laparotomy may make no difference to risk of exit site/tunnel infection
Catheter removal or replacement	RR 1.20 (0.77–1.86)	56 more per 1000 (from 65 fewer to 242 more)	167 (three RCTs)	⊕⊕⊖⊖ Low	Laparoscopy compared with laparotomy may make little or no difference to catheter removal
Technique failure	RR 0.71 (0.47–1.08)	85 fewer per 1000 (from 23 more to 155 fewer)	283 (four RCTs)	⊕⊕⊖⊖ Low	Laparoscopy compared with laparotomy make little or no difference to technique failure
All-cause mortality	RR 1.26 (0.72–2.20)	36 more per 1000 (from 39 fewer to 168 more)	270 (three RCTs)	⊕⊕⊕⊖ Moderate	Laparoscopy compared with laparotomy probably makes little or no difference to all-cause mortality

CI, confidence interval; PD, peritoneal dialysis; RCT, randomized controlled trial; RR, risk ratio.
Source: Htay and Johnson [40].

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Table 48.7 Buried (subcutaneous) compared to nonburied catheter for preventing peritonitis in PD patients.

Outcomes	Relative effect (95% CI)	Absolute effect (95% CI)	No. of participants/ patient-months (studies)	Certainty of the evidence (GRADE)	Conclusions
Peritonitis rate (patient-months)	RR 1.16 (0.37–3.60)	Six more per 1000 (from 23 fewer to 96 more)	2511 (two RCTs)	⊕⊖⊖⊖ Very low	Buried catheter has uncertain effects on peritonitis rate compared with nonburied catheter
Exit site/tunnel infection rate (patient-months)	RR 1.15 (0.39–3.42)	5 more per 1000 (from 19 fewer to 75 more)	2511 (two RCTs)	⊕⊖⊖⊖ Very low	Buried catheter has uncertain effects on exit site/tunnel infection rate compared with nonburied catheter
Technique failure	RR 0.33 (0.04–3.03)	67 fewer per 1000 (from 96 fewer to 203 more)	60 (one RCT)	⊕⊖⊖⊖ Very low	Buried catheter has uncertain effects on technique failure compared with nonburied catheter
All-cause mortality	RR 0.90 (0.39–2.08)	17 fewer per 1000 (from 103 fewer to 183 more)	119 (two RCTs)	⊕⊕⊕⊖ Moderate	Buried catheter probably makes little or no difference to all-cause mortality compared with nonburied catheter

CI, confidence interval; PD, peritoneal dialysis; RCT, randomized controlled trial; RR, risk ratio.
Source: Htay and Johnson [40].

Table 48.8 Midline compared to lateral insertion for preventing peritonitis in PD patients.

Outcomes	Relative effect (95% CI)	Absolute effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Conclusions
Peritonitis	RR 0.65 (0.32–1.33)	89 fewer per 1000 (from 84 more to 173 fewer)	120 (two RCTs)	⊕⊕⊕⊖ Moderate	Midline insertion probably makes little or no difference to peritonitis compared with lateral insertion
Exit site/tunnel infection	RR 0.56 (0.12–2.58)	35 fewer per 1000 (from 69 fewer to 124 more)	120 (two RCTs)	⊕⊕⊖⊖ Low	Midline insertion may make little or no difference to exit site/tunnel infection compared with lateral insertion
Catheter removal or replacement	RR 0.57 (0.33–0.98)	221 fewer per 1000 (from 10 fewer to 345 fewer)	83 (one RCT)	⊕⊖⊖⊖ Very low	Midline insertion has uncertain effects on catheter removal or replacement compared with lateral insertion
All-cause mortality	RR 8.50 (0.50–143.32)	0 fewer per 1000 (from 0 fewer to 0 fewer)	37 (one RCT)	⊕⊖⊖⊖ Very low	Midline insertion has uncertain effects on all-cause mortality compared with lateral insertion

CI, confidence interval; PD, peritoneal dialysis; RCT, randomized controlled trial; RR, risk ratio.
Source: Htay and Johnson [40].

CAPD Versus APD

APD is associated with a reduced risk of peritonitis compared with CAPD [24, 69] and may reflect the reduced number of connections (and therefore opportunities for intraluminal contamination). In a meta-analysis including two small, relatively short duration RCTs of APD versus CAPD, Rabindranath et al. reported that APD appeared to be superior to CAPD in reducing peritonitis rate but not risk of peritonitis or exit site/tunnel infection [70]. The results should be interpreted with caution as both studies were conducted in the 1990s, one study indicated using a Y-connector [71, 72] but the others did not specify which type of PD set was used for CAPD [71]. There is no recent RCT comparing the effects of CAPD and APD on the outcomes of peritonitis.

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Table 48.9 Straight compared to coiled catheter for preventing peritonitis in PD patients.

Outcomes	Relative effect (95% CI)	Absolute effect (95% CI)	No. of participants/ patient-months (studies)	Certainty of the evidence (GRADE)	Conclusion
Peritonitis	RR 1.04 (0.82–1.31)	Nine more per 1000 (from 39 fewer to 67 more)	818 (nine RCTs)	⊕⊕⊕⊖ Moderate	Straight catheter probably makes little or no difference to peritonitis compared with coiled catheter
Peritonitis rate (patient-months)	RR 0.91 (0.68–1.21)	Three fewer per 1000 (from seven more to 10 fewer)	5882 (five RCTs)	⊕⊕⊕⊖ Moderate	Straight catheter probably makes little or no difference to peritonitis rate compared with coiled catheter
Exit-site/tunnel infection	RR 1.12 (0.94 to 1.34)	34 more per 1000 (from 17 fewer to 95 more)	826 (10 RCTs)	⊕⊕⊕⊖ Moderate	Straight catheter probably makes little or no difference to exit site/ tunnel infection compared with coiled catheter
Exit site/tunnel infection rate (patient-months)	RR 1.05 (0.77–1.43)	One more per 1000 (from six fewer to 12 more)	5286 (four RCTs)	⊕⊕⊕⊖ Moderate	Straight catheter probably makes little or no difference to exit site/ tunnel infection rate compared with coiled catheter
Catheter removal or replacement	RR 1.11 (0.73–1.66)	27 more per 1000 (from 67 fewer to 164 more)	713 (nine RCTs)	⊕⊖⊖⊖ Very low	Straight catheter has uncertain effects on catheter removal or replacement compared with coiled catheter
Technique failure	RR 0.82 (0.51–1.31)	24 fewer per 1000 (from 41 more to 64 fewer)	442 (four RCTs)	⊕⊕⊕⊖ Moderate	Straight catheter probably makes little or no difference technique failure compared with coiled catheter
All-cause mortality	RR 0.95 (0.62–1.46)	Six fewer per 1000 (from 47 fewer to 57 more)	703 (eight RCTs)	⊕⊕⊖⊖ Low	Straight catheter may make little or no difference all-cause mortality compared with coiled catheter

CI, confidence interval; PD, peritoneal dialysis; RCT, randomized controlled trial; RR, risk ratio.
Source: Htay and Johnson [40].

PD Training

It is generally accepted that PD training and education play a critical role in prevention of PD-related infection given that proper PD training and education about safe aseptic technique during PD exchanges is considered one of the most important factors to minimize touch contamination, which is the commonest cause of PD-related infection. There are several observational studies on the PD training-related activities, focusing on the number of training hours, trainer experience, ratio of trainers to patients, method/ principle of teaching used for training, and role of retraining on the outcomes of PD patients, including infection-related outcomes (such as peritonitis or exit site/tunnel infection) and noninfection outcomes [73–78]. However, there are no well-conducted RCTs examining the effects of PD training-related activities on infection related outcomes in PD patients. Future RCTs examining the PD training related activities on infection and noninfection related outcomes are needed.

Summary

Interventions that have been shown to be of benefit in prevention of PD-related infection include intravenous prophylactic antibiotics prior to catheter insertion, use of prophylactic topical antimicrobial agents, Y-set or double bag system, and antifungal prophylaxis during antibiotic therapy.

Treatment

Peritonitis causes high morbidity, technique failure, and mortality [46]. Early and prompt treatment of peritonitis is crucial to reduce these complications and improve technique and patient survival. Exit site/tunnel infection can progress to peritonitis [79, 80]. Early and effective treatment of exit site/tunnel infection is important to prevent infection-related technique failure in PD patients.

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The mainstay of treatment in PD-related infection is medical therapy (intraperitoneal antimicrobial agents), with surgical intervention reserved for failure to respond to medical therapy (Table 48.1).

Exit Site and Tunnel Infections

Management of exit site/tunnel infection is important as it has been shown to lead to peritonitis and technique failure [80]. ISPD recommends prompt treatment of exit site/tunnel infection to reduce subsequent peritonitis [4]. In addition, ISPD recommends daily cleaning of the exit site during ESI [4]. The role of topical antimicrobial agents in the treatment of exit site/tunnel infection is uncertain given that there has been no RCT conducted on this subject.

There is paucity of study on the treatment of catheter exit-site/tunnel tract infection in PD patients, as most studies emphasize the prevention of exit site/tunnel tract infection. To date, there are two RCTs comparing the different types of antibiotics or route of administration on the treatment of exit site/tunnel infection and both studies were published in the 1990s [81, 82]. Plum et al. conducted a randomized study of oral versus intraperitoneal (IP) administration of clindamycin on 16 CAPD patients with clinically and ultrasound proven tunnel infections and reported that the IP route was superior to the oral route based on resolution of peri-catheter abscess by ultrasound criteria [82]. However, Flanigan et al. conducted a randomized study comparing the effect of a combination of IP vancomycin and oral rifampin versus oral trimethoprim/sulfamethoxazole for treatment of exit site/tunnel infection and reported that the percentage of cure for *Staphylococcal* infections was comparable between the two groups [81]. It is difficult to draw conclusions from these two studies given the small sample size and different antibiotics used between studies.

ISPD recommends empiric oral antibiotics covering *S. aureus,* such as penicillinase-resistant penicillin or first-generation cephalosporin, to be used to treat exit site/tunnel infection unless patients have a prior history of methicillin-resistant *S. aureus* (MRSA) or Pseudomonas species, in which case appropriate antibiotics, such as glycopeptide or clindamycin for MRSA carriers and anti--*pseudomonal* antibiotics for patients with prior history of Pseudomonas infection, should be prescribed [4, 16].

There is no RCT to date examining the effect of antibiotic duration on the outcomes of exit site/tunnel tract infection in PD patients. ISPD recommends 2 weeks of antibiotics for non-*Pseudomonal* exit site/tunnel infection and 3 weeks for infection with *Pseudomonal* species [4, 16].

ISPD recommends catheter removal in refractory exit site/tunnel infection, defined as failure to response to medical therapy despite appropriate antibiotics for 3 weeks, catheter infection that leads to peritonitis or catheter infection that occurs simultaneously with peritonitis [4].

Peritonitis

Early and effective management of peritonitis is important to reduce the risk of adverse outcomes, such as catheter removal. The mainstay of treatment is antimicrobial therapy, although adjunctive therapies have been employed, including the use of fibrinolytic agents [13, 83, 84], peritoneallavage [85], and routine early catheter removal [86].

Empirical Antibiotic Therapy

Once peritonitis has occurred, the ISPD and KHA-CARI guidelines both state that empirical therapy with antibiotics that will cover both Gram-negative and Gram-positive organisms should be initiated at the time a diagnosis of peritonitis is suspected [4, 16, 87].

Specific antibiotic agents are not recommended, although the ISPD guidelines suggest that local patterns of causative organisms and bacterial resistance should be taken into consideration by each center. Following identification of a specific organism, targeted therapy should be initiated [16].

Antibiotic Regimens

The Cochrane review group did not identify any optimal antibiotic agent or combination of agents [44]. IP glycopeptides (vancomycin or teicoplanin) had uncertain effects on primary treatment response, relapse rates, and need for catheter removal compared to first-generation cephalosporin (Table 48.10), although glycopeptide regimens were more likely to achieve a complete cure [44].

A large number of antibiotic regimens used in the treatment of peritonitis have been evaluated in RCTs [88–90]. Only two antibiotic regimens were found to be superior in a systematic review [44]. However, in both cases the applicability to current practice is low. Meta-analysis of two trials comparing cefazolin and vancomycin found vancomycin to be superior at achieving complete cure [44]. This finding was strongly influenced by a large number of patients in one trial in which a low dose of cefazolin (50 mg/l) was used [88]. The other trial included in the meta-analysis used a cefazolin dose of 125 mg/l [90], as is recommended in the ISPD guidelines, and found the two agents to be equivalent. IP ciprofloxacin/rifampicin was

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Table 48.10 First-generation cephalosporin compared to glycopeptide-based IP antibiotic regimen for PD-associated peritonitis.

Outcomes	Relative effect (95% CI)	Absolute effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Conclusions
Failure to achieve complete cure	RR 1.66 (1.01–2.72)	131 more per 1000 (from 2 more to 342 more)	370 (three studies)	⊕⊕⊖⊖ Low	Use of first-generation cephalosporin regimen may probably fail to achieve complete cure than glycopeptide or teicoplanin based regimen
Failure to achieve complete cure	RR 1.51 (1.03–2.22)	120 more per 1000 (from seven more to 288 more)	305 (two studies)	⊕⊕⊖⊖ Low	Use of first-generation cephalosporin regimen may probably fail to achieve complete cure than glycopeptide-based regimen
Primary treatment failure	RR 1.14 (0.69–1.87)	22 more per 1000 (from 50 fewer to 139 more)	305 (two studies)	⊕⊖⊖⊖ Very low	It is uncertain that first-generation cephalosporin regime increases primary treatment failure compared with glycopeptide-based regimen
Relapse	RR 1.62 (0.69–3.79)	47 more per 1000 (from 24 fewer to 213 more)	305 (two studies)	⊕⊖⊖⊖ Very low	It is uncertain that first generation cephalosporin regime increases relapsing peritonitis compared with glycopeptide-based regimen
Catheter removal	RR 0.95 (0.41–2.19)	Eight fewer per 1000 (from 94 fewer to 190 more)	305 (two studies)	⊕⊖⊖⊖ Very low	It is uncertain that first-generation cephalosporin regime reduces catheter removal compared with glycopeptide-based regimen

CI, confidence interval; IP, intraperitoneal; PD, peritoneal dialysis; RR, risk ratio.
Source: Ballinger et al. [44].

found to be superior to IP cephradine in one trial [91]. The usefulness of this finding is limited by the use of monotherapy with a first-generation cephalosporin in one treatment arm, without any broad Gram-negative cover, a practice which is now uncommon. Similarly, first-line use of ciprofloxacin and rifampicin is restricted in many centers due to concerns regarding the risk of emergence of multiresistant organisms. In summary, there is limited evidence that any specific antibiotic regimen is superior to others in reducing primary treatment failure or relapsing peritonitis in PD patients.

No currently available guidelines recommend specific antibiotic regimens, reflecting the paucity of available evidence, although information regarding factors requiring consideration when selecting antibiotics is provided. ISPD Guidelines recommend that there should be center-specific selection of agents according to local causative microorganism and resistance patterns [16]. The impact of local microbial resistance on peritonitis outcomes was apparent in two trials comparing oral and intraperitoneal quinolone use. In both studies, response rates were low for both treatment arms (41.7% and 55.6% in the oral group and 66.7% and 70.6% in the intraperitoneal group, respectively) [92]. Microorganism resistance to quinolones was the major cause of treatment failure, and previous exposure to quinolones was a risk factor for infection with resistant microorganisms. Similarly, the emergence of VRE is associated with use of broad-spectrum antibiotics [93, 94].

Duration of Antibiotics

Longer duration treatment (21 days of IV vancomycin and IP gentamicin) had uncertain effects on risk of treatment relapse compared with 10 days of treatment (one study, 49 patients, RR 1.56, 95% CI 0.60–3.95) [44].

Route of Antibiotic Administration

The optimal route of antibiotic administration was addressed in trials comparing oral and intraperitoneal administration [92, 95], and IV and IP dosing [96]. IP antibiotics were superior to IV antibiotics in reducing treatment failure in one small study (RR 3.52, 95% CI 1.26–9.81) where the initial antibiotics were given intravenously, followed by oral antibiotics at day 4 if considered appropriate [44]. This finding may relate to achievement of higher intraperitoneal antibiotic concentrations with intraperitoneal administration compared to systemic dosing and early use of oral therapy, however a meta-analysis of 10 trials found that oral dosing was equivalent to intraperitoneal dosing [44]. This was demonstrated when the same drug was administered intraperitoneally and per oral, and when oral quinolone monotherapy was compared to IP combination therapy [92].

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Intermittent Versus Continuous Antibiotic Administration

An intermittent dosing regimen has uncertain effects on complete cure (four studies, 338 participants, RR 0.92, 95% CI 0.64–1.33), primary treatment failure (five studies, 522 participants, RR 1.11, 95% CI 0.77–1.62) and risk of relapse (four studies, 338 participants, RR 0.76, 95% CI 0.45–1.28) compared with a continuous dosing regimen [44] (Table 48.11). The applicability of results from trials of intermittent drug therapy in CAPD to APD is unclear. Drug half-lives are greater and clearance more rapid in cycler dwells compared to noncycler dwells [97]. Pharmacokinetic studies of IP antibiotic dosing suggest that therapeutic drug levels are achieved during 6-hour dwells, therefore it is likely that a patient can remain on APD as long as there is at least a 6-hour daytime dwell [97, 98] during which antibiotics can be administered.

Peritoneal Lavage

Peritoneal lavage in conjunction to antibiotic treatment has uncertain effects on improvement in treatment response to antibiotic therapy [44].

Urokinase

Urokinase had no advantages over placebo in improving response rates or reducing relapse and, when compared to early catheter removal, urokinase was clearly inferior in reducing treatment failure for relapsing or persistent peritonitis [44].

Intraperitoneal Immunoglobulin

One study of intraperitoneal immunoglobulin administration in conjunction with antibiotics found that the treatment group achieved biochemical and clinical parameters of improvement sooner and that the duration of antibiotic therapy was shorter [14]. However, the response rate was 100% in both groups with no relapses during a 3-month follow-up period, suggesting that use of immunoglobulin does not change overall patient outcomes. This, together with the expense and limited availability of immunoglobulin therapy, reduces the feasibility of this treatment as part of routine therapy at the present time.

Table 48.11 Intermittent compared to continuous antibiotics for peritoneal dialysis-associated peritonitis.

Outcomes	Relative effect (95% CI)	Absolute effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Conclusions
Failure to achieve complete cure	RR 0.92 (0.64–1.33)	21 fewer per 1000 (from 85 more to 93 fewer)	338 (four studies)	⊕⊖⊖⊖ Very low	Intermittent IP dosing has uncertain effects on complete cure compared with continuous IP dosing
Failure to achieve complete cure - gentamicin	RR 0.79 (0.45–1.37)	80 fewer per 1000 (from 141 more to 209 fewer)	100 (one study)		Intermittent IP dosing of gentamicin has uncertain effects on complete cure compared with continuous IP dosing
Failure to achieve complete cure - vancomycin	RR 0.62 (0.18–2.11)	59 fewer per 1000 (from 128 fewer to 173 more)	72 (two studies)	⊕⊖⊖⊖ Very low	Intermittent IP dosing of vancomycin has uncertain effects on complete cure compared with continuous IP dosing
Primary treatment failure	RR 1.11 (0.77–1.62)	17 more per 1000 (from 37 fewer to 99 more)	522 (five studies)	⊕⊖⊖⊖ Very low	Intermittent IP dosing has uncertain effects on primary treatment failure compared with continuous IP dosing
Primary treatment failure - gentamicin	RR 0.67 (0.26–1.73)	59 fewer per 1000 (from 131 more to 133 fewer)	100 (one study)		Intermittent IP dosing of gentamicin has uncertain effects on primary treatment failure compared with continuous IP dosing
Primary treatment failure - vancomycin	RR 1.10 (0.08–15.36)	Three more per 1000 (from 29 fewer to 449 more)	72 (two studies)	⊕⊖⊖⊖ Very low	Intermittent IP dosing of vancomycin has uncertain effects on primary treatment failure compared with continuous IP dosing

CI, confidence interval; IP, intraperitoneal; RR, risk ratio.
Source: Ballinger et al. [44].

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Catheter Removal

ISPD recommend catheter removal for refractory and relapsing peritonitis, fungal peritonitis, and some cases where there is no response to therapy [4, 16]. KHA-CARI makes no recommendation about the timing of catheter removal due to lack of evidence but do state that catheter removal is superior to urokinase [87].

For relapsing or persistent peritonitis, simultaneous catheter removal and replacement was better than prolinase at reducing treatment failure rates although evidence was limited to a single small study [86]. There have been no clinical trials evaluating the role of routine early catheter removal in refractory peritonitis, or of temporary transfer of patients from APD to CAPD. In the latter case, the question of when to safely recommence APD has also not been addressed.

Surgical peritonitis refers to cases when peritonitis arises from intraabdominal pathology. This may manifest as polymicrobial peritonitis. Such cases are usually treated by laparotomy and catheter removal at the same time as the underlying pathology is addressed, followed by a course of broad-spectrum intravenous antibiotics. There have been no trials addressing the treatment of this situation, and such trials are unlikely to be performed.

Summary

Even though PD-related infection has a significant impact on patient outcome, trials and reviews examining interventions to prevent infections have been limited by suboptimal methodological quality. There is also a paucity of evidence-based recommendations for treating exit site/tunnel infection in PD patients. For treatment of PD peritonitis, a glycopeptide-based regimen may increase complete cure but exerts uncertain effects on primary treatment failure, relapse, and catheter removal compared with a first-generation cephalosporin. The intraperitoneal route may increase complete cure and reduce primary treatment failure compared with oral or intravenous route of administration of antibiotics during peritonitis. An intermittent dosing regimen has uncertain effects on treatment outcomes compared with a continuous dosing regimen. Peritoneal lavage has uncertain effects on outcomes of peritonitis. Simultaneous catheter removal and replacement may reduce recurrent peritonitis compared with urokinase in patients with recurrent peritonitis. In general, review conclusions were based on a small number of studies with few events in which the risk of bias was generally high, interventions were heterogeneous, and outcome definitions were often inconsistent. There were no RCTs evaluating optimal timing of catheter removal and data for APD were absent.

Definitions of peritonitis, successful treatment and relapse varied between trials thereby reducing their comparability. Similarly, antibiotic doses were not consistent across studies. The follow-up period of most included trials was 28 days or less meaning that several long-term outcomes of peritonitis treatment, such as technique failure and longer-term mortality, were not evaluated. Studies tended to focus on choice and route of antibiotic without consideration of other variables, such as total duration of therapy or drug dose. To date, there have been no RCTs of treatment for fungal peritonitis, a condition that is associated with almost 100% catheter loss and high levels of mortality. Trials often predated the current era of lower peritonitis rates, newer antibiotic therapies, and increased awareness of multiresistant organisms, thereby potentially reducing the applicability of our meta-analyses or the individual trials' results. These aspects all need to be considered when making a decision about recommending or suggesting adoption of these interventions.

Conclusions

In summary, prophylactic intravenous antibiotic prior to PD catheter insertion may prevent early peritonitis, application of topical mupirocin application may reduce exit site/tunnel infection and peritonitis, use of Y-set or double bag systems reduces peritonitis but not ESI, and concomitant use of antifungal prophylaxis with antibiotic therapy may prevent fungal peritonitis. Methods of catheter insertion, types of catheter or immobilization of catheter have uncertain effects on exit site/tunnel infection or peritonitis. With regards to treatment of peritonitis, the available evidence suggests that glycopeptide-based regimens may increase complete cure but have uncertain effects on primary treatment failure, relapse or catheter removal compared with a first-generation cephalosporin regimen. Empirical antibiotic treatment regimens are similar in efficacy to each other, such that no specific regimen can be recommended. The intraperitoneal route may increase complete cure and reduce primary treatment failure compared with oral or intravenous antibiotics. An intermittent dosing regimen has uncertain effects on infection-related outcomes compared with a continuous dosing regimen. Peritoneal lavage or urokinase therapy has uncertain effects on complete cure, relapse or technique failure. When dealing with recurrent peritonitis, simultaneous catheter removal or replacement may reduce recurrent peritonitis compared with urokinase therapy.

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49

Urgent-start Peritoneal Dialysis

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Introduction

Across the world, there is an increasing growth in the number of patients with end-stage kidney disease, with over 2 million people receiving renal replacement therapy worldwide [1]. Peritoneal dialysis (PD) has several advantages over hemodialysis (HD), including preservation of vasculature for future dialysis access [2], an initial survival advantage [3, 4], cost effectiveness [5], and preservation of residual renal function [6, 7]. From a patient's perspective, there is also a greater level of satisfaction and quality of life, as well as an enhanced flexibility to travel [8–10]. Moreover, initiating patients on PD is associated with a significantly lowered risk of death compared to hemodialysis with a central venous catheter (CVC) in the first year after dialysis initiation [11].

Despite several clinically important and patient-centered advantages of PD, its uptake has been static or declining in some parts of the world [8, 12, 13]. One of the main barriers to broader utilization of PD has been reluctance to initiate PD in settings where dialysis access has not been established [14]. About 80% of patients commence dialysis using a CVC due to a lack of established dialysis access [15–18], despite well-known complications associated with use, including association with all-cause mortality, hospitalization, fatal infections, and cardiovascular events [19–21]. The prevalence of CVC usage has remained relatively unchanged over the last decade in countries such as the United States, with frequencies exceeding 80% of all hemodialysis access types in 2006 according to the US Renal Data System (USRDS) report, with similar usage reported in 2015 [22, 23]. These trends have not been effectively mitigated by implementation of targeted strategies, including an incentivized government-funded scheme to reward units achieving reductions in CVC-utilized dialysis [24].

Once established on center or satellite hemodialysis via CVC, patients are also less likely to undergo modality transfer to PD [25, 26]. Reluctance to utilize PD under these clinical contexts stems from a recommendation from the International Society for Peritoneal Dialysis (ISPD) to avoid initiation of PD for at least 2 weeks after insertion of a PD catheter to reduce the risk of catheter-related complications [27]. This practice is supported by results from several studies [27, 28], including a recently completed randomized controlled trial involving 122 PD patients [29], which showed an increased risk of catheter-related complications, such as leaks, when PD was initiated earlier than 2 weeks after catheter insertion. There is increasing evidence that the long-term outcomes of PD patients managed with early catheter access are comparable to those who received conventional-start PD [30–32].

Consequently, in patients who require urgent initiation of dialysis without established dialysis access, there has been emerging support for expedited initiation of PD prior to reaching the 2-week break-in period milestone [30, 33–35], referred to as *urgent-start PD*. This initiative has been introduced as an effective alternative for patients commencing unplanned dialysis with several aims, including reduced patient harm through avoidance of CVC insertion, increased utilization of home-based dialysis, and

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enhanced cost-effectiveness. In this chapter, we will summarize the evidence to date regarding the definition, prevalence, and outcomes of urgent-start PD.

Definition

A universal definition of urgent-start PD does not currently exist in the literature (Table 49.1). Urgent-start PD is most commonly defined as the initiation of PD within 2 weeks of PD catheter insertion in a patient who is not yet established on any form of renal replacement therapy and does not have established dialysis access available for use [30, 31, 39–42]. However, the time period criterion used to define urgent-start PD has been variably reported in the literature, ranging from immediately after PD catheter insertion to up to 14 days [28, 34, 35, 39, 41, 43].

Alkatheeri et al., from Ontario, Canada, have reported their experience in initiating an urgent-start PD program involving 30 PD patients in their unit, whereby urgent-start PD was defined as commencement of PD within 2 weeks of insertion depending on the patient's condition or indication for dialysis [42]. The median time interval between PD catheter insertion and initiation was 6 days [42], and 20% of these patients required immediate-start PD following catheter insertion due to uremic symptoms and/or severe volume overload [42]. Dias et al. from Brazil conducted a single-center observational study reporting outcomes in 35 patients with end-stage kidney disease who required PD initiation within 72 hours after PD catheter insertion [43]. The indications for urgent dialysis included uremia, fluid overload, hyperkalemia ($K > 6.5$ mmol/l), and metabolic acidosis ($HCO_3 < 10$ mmol/l) that were refractory to clinical measures. Other investigators incorporated these clinical criteria and defined a subgroup within the urgent-start PD cohort, referred to as immediate-start [42] or emergent-start PD [30, 41, 42, 44], whereby dialysis was required within 24–48 hours after initial clinical assessment. Patients categorized into these groups were treated with either PD [42] or temporary hemodialysis via a CVC line to achieve clinical stabilization prior to being reactivated in the urgent-start PD pathway [30]. Other groups have variably treated patients with an unplanned dialysis requirement using hemodialysis prior to progressing into the PD pathway and without adopting a clear definition of timeline or clinical indication [35]. As the time interval between PD catheter insertion and initiation can impact on the risk of early complications, it is important to be aware of how urgent-start PD was defined in these studies until a universally agreed definition can be determined.

Table 49.1 Urgent-start peritoneal dialysis.

Treatment	Recommendation	Certainty of evidence	Strength of recommendation
Urgent-start PD compared with conventional-start PD	We suggest that for patients with end-stage kidney disease who require urgent dialysis and are suitable for PD, urgent-start PD can be considered to avoid HD via a central venous catheter. Although urgent-start PD may increase the likelihood of dialysate leak, it has uncertain effects on catheter malfunction, exit-site infection, peritonitis, technique, and patient survival compared with conventional-start PD.	Low (dialysate leak) Very low (catheter blockage, catheter malposition, catheter readjustment, exit-site infection, peritonitis, technique survival, and mortality)	Weak [36]
Urgent-start PD compared with urgent-start HD	We suggest that urgent-start PD can be considered for patients with end-stage kidney disease who require urgent dialysis and are suitable for PD because urgent-start PD may reduce the risk of bacteremia compared with urgent-start HD. Urgent-start PD has uncertain effects on catheter malfunction, catheter readjustment, exit-site infection, peritonitis, technique, and patient survival compared with urgent-start HD.	Low (bacteremia) Very low (catheter malfunction, catheter readjustment, exit-site infection, peritonitis, technique survival, and mortality)	Weak [37]

GRADE assessment of the certainty of the evidence [38]: High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different* is low. Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different* is moderate. Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different* is high. Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different* is very high. *Substantially different = a large enough difference that it might affect decision-making.
HD, hemodialysis; PD, peritoneal dialysis.

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In summary, urgent-start PD is most commonly defined as the requirement to initiate PD within 2 weeks of PD catheter insertion in patients who require unplanned dialysis. Depending on urgency or clinical stability, investigators have variably further distinguished patients requiring immediate- or emergent-start dialysis who received PD or temporary hemodialysis depending on their local protocol or practice pattern.

Epidemiology

Povlsen and Ivarsen were two of the earliest researchers to describe a dedicated urgent-start PD program in Denmark [28]. Between 2000 and 2002, 52 patients commenced PD within 24 hours of catheter insertion [28]. Since then, there has been growing evidence and literature on the topic, with most outcomes reported from single-center studies [30, 33–35, 42, 45, 46], publishing their clinical experience without a standardized approach in the delivery of therapy or even an agreed definition of urgent-start PD. There are currently no reported data to ascertain the global uptake of urgent-start PD programs.

To our knowledge, the largest observational cohort study conducted to date was in China, with 922 patients who initiated urgent-start PD from January 2003 to May 2013, defined as commencing PD within 1 week after PD catheter insertion [47]. PD catheters were inserted under local anesthesia using an open surgical approach by a nephrologist. Almost half of the patients initiated PD within 24 hours of catheter insertion due to the presence of indications for acute dialysis [47].

Whilst delivery of urgent-start PD has been described in both higher income [31, 33, 48] and lower income [43] countries, the majority of the literature originates from countries in North America, Asia, Europe, and Australia (Table 49.1) [30, 31, 34, 35, 39, 41, 42]. Most studies have reported their experience in commencing PD prior to reaching the 2-week milestone after PD catheter insertion without an increase in infrastructural support to formally implement urgent-start PD program in their institutions [31, 34, 45, 46].

A barrier to broader uptake of urgent-start PD may be attributable to physician practice patterns, which may be largely contributed to by a lack of adequate resources necessary to execute urgent-start PD [12, 49]. While most medical centers are well equipped for providing emergent or urgent hemodialysis for patients by using interventional radiology for CVC insertion with available nursing staff, it is less common to have a dedicated team to deliver urgent-start PD. Pioneers of urgent-start PD programs have previously emphasized the need for novel infrastructure to establish urgent-start PD programs [33, 50]. For example, Alkatheeri et al. reported their experience in initiating an urgent-start PD program in July 2010, which involved an international nephrologist, a surgeon, a dedicated urgent-start PD case manager, and a dialysis access coordinator [42]. Patients who were identified as being suitable for urgent-start PD were assessed by a dedicated team within 24 hours of referral and, if eligible, were offered urgent-start PD whereby a PD catheter was inserted either percutaneously by an interventional nephrologist or laparoscopically by a general surgeon. All patients initiated PD within 2 weeks of insertion, depending on their condition or indication for dialysis [42], either as an inpatient or outpatient. Successful implementation of the program led to a significant increase in the size of their PD patient population from 90 to 133 patients in 3 years [42].

Patient Selection

Patients who have received urgent-start PD have largely been those who were referred late to the nephrology service [30, 31, 47] without adequate predialysis education and preparation. Under such circumstances, the decision to undertake PD has often needed to be made quickly as a result of symptomatic uremia or fluid overload [30] without sufficient opportunity to receive education or a home visit to verify the appropriateness of PD. To ensure suitable patient selection, Ghaffari et al. have developed and successfully applied a "Predialysis patient questionnaire: modality selection" in their program in the United States [30]. The 15 questions cover areas including status of dialysis education, work/home situation, and medical/surgical history. Based on the answers, the physician in charge of the urgent-start PD program determines the appropriateness of PD in patients in need of urgent-start dialysis. From embedding a formally protocol-based pathway, there was 100% retention of urgent-start PD patients on PD during follow-up with growth in their PD program by 37.5% in 12 months after commencement of the urgent-start PD initiative [30].

Catheter Insertion

There have been varying approaches to catheter insertion among the different urgent-start PD programs reported. Two Chinese studies involving 657 and 178 patients adopted insertion of a PD catheter by nephrologists via a laparotomy approach [46, 51], similar to that of other reported studies [28, 47]. To minimize the risk of leaks from early access of the PD catheter, some groups have

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inserted PD catheters via a surgical technique using purse-string sutures to fixate the peritoneum to the catheter [52]. Other groups from the United States [30], Canada [42], and Singapore [53] had PD catheters inserted by interventional radiologists. Where catheters could not be inserted fluoroscopically, laparoscopic insertion by surgeons took place [42]. Varying insertion approaches were adopted largely due to local expertise availability, resources, and beliefs regarding the association between catheter insertion techniques and risks of early complications [30, 42, 46]. A recent randomized controlled trial comparing open and laparoscopic insertion of PD catheters observed similar outcomes in patients with regards to the risk of complications [54]. However, this study was in patients initiating PD 2–4 weeks after catheter insertion, and therefore may not be applicable to urgent-start PD patients [54].

Urgent-start PD Prescription

The reported approaches to delivering urgent-start PD have been variable with regards to PD modality (continuous ambulatory PD [CAPD] vs. automated PD [APD]), fill volume, and treatment delivery frequency. Most commonly, studies have adopted a protocol utilizing intermittent PD in the supine position with low initial intraperitoneal fill volumes [30, 31, 34, 46, 48] to reduce the risks of PD catheter leaks and infections through lowered intra-abdominal pressure [55]. Ghaffari et al. reported a detailed prescription using intermittent peritoneal dialysis, administered three times a week, and calculated the volume and number of exchanges based of the modification of diet in renal disease estimated glomerular filtration rate (MDRD eGFR) and body surface area (BSA). Fill volumes ranged from 500 to 1000 ml, four to six cycles were utilized, and various combinations of 1.5%, 2.5%, and 4.25% dextrose exchanges were used, depending on the patient's volume status [30]. For example, an initial fill volume of 500 ml/exchange was used for patients with BSA $< 1.65/m^2$ compared to 1000 ml for those with BSA $> 1.8/m^2$ [30]. The duration of total cycler time and number of cycles varied depending on the baseline MDRD eGFR and BSA, and the frequency of therapy was generally thrice weekly unless more frequent treatment was indicated [30].

A smaller number of studies have reported using CAPD in their delivery of urgent-start PD [47, 51]. Liu and colleagues from China have recently published their experience with urgent-start PD delivered using three different treatment approaches, including traditional incremental CAPD ($n = 26$), APD ($n = 42$), and combined APD-CAPD ($n = 28$) in patients who commenced PD within 1–3 days after open surgical PD catheter insertion. PD prescription varied in the three groups, but fill volume was not determined by body size. For example, the initial regimen in the APD group included nine cycles of 650 ml fill volume during the day with an overnight dwell for the first 3 days, eight cycles of 1000 ml with an overnight dwell on days 4–6, then finally six cycles of 1500 ml with an overnight dwell on days 7–9. In contrast, the CAPD group received four cycles of 500–800 ml fill volumes, which gradually increased to 1000 and 1500 ml fill volumes within the first 9 days. The APD-CAPD group were initiated with the regimen described for the APD group for the first 6 days followed by CAPD during the subsequent 3 days (four cycles of 1.5 l over 4 hours with an overnight dwell) [56]. Although the investigators reported better small solute clearance in APD initiated patients ($P < 0.05$) with a comparable risk of complications ($P > 0.05$), the findings were potentially limited by indication bias with residual confounding given the retrospective observational design of the study.

The majority of studies have reported initiating urgent-start PD with fill volumes less than 1.2 l [31, 42, 45]. However, some studies have utilized an initial fill volume of up to 2 l, commencing within the first 24 hours after PD catheter insertion by nephrologists, as reported in a randomized controlled trial [57]. The use of full volume dialysate (2 l) at day 1 was compared to incremental dialysate volumes with CAPD exchanges starting at 500 ml for the first 6 days then gradually increasing to the full volume exchanges at 2 weeks. It was shown that dialysate leaks occurred at a similar rate in both groups with 10.5% of patients in the full volume group developing leaks compared to 9.5% in the incremental group. Overall, the short- and long-term outcomes from patients who received initial fill volumes of 2 l were comparable with those of the stepwise incremental protocol [57].

In summary, the studies to date have reported varying approaches to the prescription of urgent-start PD. While there are some studies comparing PD modalities and different fill volumes, urgent-start PD is still lacking an overall evidence-based guideline for optimal prescription and initiation of the treatment.

Outcomes

The outcomes of patients undergoing urgent-start PD program can be broadly compared to those of patients receiving conventional-start PD or urgent-start hemodialysis via a CVC, and further classified according to early- and late-outcomes in each of these groups (see Table 49.2).

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Table 49.2 Definition.

Study	Year	Country	Study design	Study Population	Definition of urgent-start PD	Emergent dialysis
			Unplanned HD vs. urgent-start PD			
Koch et al. [34]	Jan 2004-Dec 2006	Germany	Prospective, observational	Unplanned HD ($n = 57$) vs. unplanned PD ($n = 66$)	Unplanned dialysis required urgently without established access (no time given)	–
Jin et al. [45]	Jan 2011 –Dec 2014	China	Retrospective, observational	Unplanned HD ($n = 41$) vs. unplanned PD ($n = 53$)	Requiring initiation of dialysis <2 weeks after catheter placement	Severe hyperkalemia (>6.5 mmol/), severe hypertension, severe acidosis (bicarbonate <12 mmol/l), severe respiratory insufficiency or severe heart failure (these patients were excluded from the study)
Jin et al. [51]	Jan 2013–Dec 2014	China	Retrospective, observational	Unplanned HD ($n = 82$) vs. urgent-start PD ($n = 96$)	Starting PD within 14 days of PD catheter placement	Severe hyperkalemia (>6.5 mmol/l), severe acidosis (bicarbonate <12 mmol/l), severe respiratory insufficiency or severe heart failure (these patients were excluded from the study).
Dayana Bitencourt Dias [43]	Jul 2014–Jul 2015	Brazil	Prospective study	Unplanned HD ($n = 49$) vs. unplanned PD ($n = 51$)	Initiation of PD within 72 h of peritoneal catheter placement	–
			Urgent-start PD vs. conventional-start PD			
Povlsen and Ivarsen [28]	Jan 2000–Jun 2002	Denmark	Retrospective	Urgent-start PD ($n = 52$) vs. planned-start PD ($n = 52$)	Initiation of PD <24 h of catheter placement	
Povlsen et al. [39]	2005–2009	Denmark	Prospective, observational	Urgent-start PD ($n = 338$) vs. planned PD ($n = 255$)	Initiation PD 0–14 days after PD catheter implantation	–
Yang et al. [32]	2010	Taiwan	Retrospective with unmatched controls	Early-start incremental PD ($n = 226$) vs late-start PD ($n = 84$)	Starting PD <14 days within catheter placement	
Ghaffari [30]	Mar 2010–2011	United States	Prospective, observational	Urgent-start PD ($n = 18$) vs conventional-start PD ($n = 9$)	Requiring dialysis less than 2 weeks	Need for dialysis <48 h
See et al. [31]	Jan 2010–Jun 2015	Australia	Single-center, matched case control study	Urgent-start PD ($n = 26$) vs conventional-start PD ($n = 78$)	Initiation PD within 2 weeks of catheter insertion	–

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Emergent-start PD vs. urgent-start PD/conventional-start PD						
Kim, S et al. [40]	Jan 2007–Dec 2014	Republic of Korea	Retrospective	Break-in period: <48 h ($n = 103$) vs. break-in period 2–13 days ($n = 87$)	BUN >100, creatinine >10 mg/dl, $K > 6$ mEq/l or pulmonary oedema with break-in period <2 weeks	–
Wong et al. [41]	Jul 2013–Feb 2015	United States	Observational	Emergent vs. nonemergent (urgent-start PD)	Initiating dialysis within 14 d of PD catheter placement	Initiation dialysis <48 h
Nayak et al. [44]	Mar 2016–Aug 2017	India	Prospective, case-controlled study	Emergent PD ($n = 32$) vs conventional-start PD ($n = 24$)	–	Initiation of PD within 48 h of presentation
Urgent-start PD						
Xu et al. [47]	Jan 2003–May 2013	China	Observational cohort study	Urgent-start PD patient ($n = 922$) Acute dialysis indication ($n = 164$), defined	Initiation of PD therapy within 7 days of catheter insertion	Initiated PD on day of catheter placement due to hyperkalemia, uremic encephalopathy, bicarbonate <15 mmol/l, congestive heart failure, several metabolic acidosis
Alkatheeri et al. [42]	Jul 2010–Oct 2013	Canada	Prospective, observational	Urgent-start PD patients ($n = 30$) Patients starting PD <24 h ($n = 6$)	Dialysis within 2 weeks of PD catheter insertion	PD within 24 h due to uremia or fluid overload
Casaretto et al. [33]	Jan 2011–Dec 2011	United States	Observational report	Urgent-start PD patients ($n = 11$)	Dialysis initiated within 24 h (two patients) or within 2 days (two patients)	–
Masseur et al. [58]	Jan 2011–Sep 2013	United States	Prospective, observational	Urgent-start PD patients ($n = 81$)	Initiation of PD <14 days of catheter placement	–

BUN, blood urea nitrogen; HD, hemodialysis; PD, peritoneal dialysis.

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Urgent-start PD vs. Conventional-start PD

Unlike conventional-start PD when initiation of therapy is delayed until at least 2 weeks after catheter insertion to promote wound healing, earlier treatment initiation has raised concerns about an increase in the risk of mechanical complications, such as peri-catheter leaks (Tables 49.3, 49.4a, and 49.4b). The likelihood of developing these complications may also be influenced by insertion technique, duration between catheter insertion, and PD commencement (e.g. immediate vs. 7 days), fill volume or modality of dialysis delivery (CAPD vs. APD) [59, 60]. Moreover, the characteristics of patients undergoing urgent-start PD program may be inherently different from those receiving planned conventional PD treatment. See et al. have previously conducted a 1 : 3 matched case-control study involving 26 urgent-start and 78 conventional-start PD patients [31]. The patients were well-matched on age (50.6 ± 13 years vs. 51 ± 14.5 years, $P = 0.9$) and diabetic status (35% vs. 35%, $P = 1.0$) at the time of PD initiation. Compared to conventional-start PD patients, those who

Table 49.3 Urgent-start PD versus conventional-start PD.

Study	Design	Study population	Outcomes	Results
Povlsen and Ivarsen [28]	Retrospective, observational with unmatched controls	Group 1: urgent-start PD ($n = 52$) Group 2: conventional-start PD ($n = 52$)	Catheter-related complications (short term): Technique survival, mechanical complications, infectious complications	Technique survival: • G1 86.7% vs. G2 90% Catheter replacement: • G1 19.2% vs. G2 3.9% Total mechanical complications: • G1 28.9% vs. G2 7.7% Infections: no difference
Yang et al. [32]	Retrospective with unmatched controls	Urgent-start PD ($n = 226$) vs. conventional-start PD ($n = 84$)	Catheter-related complications within 6 months of catheter insertion	Urgent-start PD vs. conventional-start PD: • Complications: 14.6% vs.13.1% (NS) • Bridge hemodialysis 31.4% vs. 57.1% • Peritonitis 4% vs. 2.4%
Ghaffari [30]	Prospective, observational	Urgent-start ($n = 18$) vs. planned-start PD ($n = 9$)	Complications (peritonitis, catheter leaks, and malfunction, exit site infection) Clinical outcomes (PTH, albumin, Kt/V, hemoglobin, iron studies, phosphate, and calcium)	Urgent-start vs. planned-start PD • Minor catheter leaks: 4% vs. 1% • Peritonitis: 1% vs. 1% • Malfunction 2% vs. 2% Short-term clinical outcomes similar between the two groups
Liu et al. [46]	Retrospective observational	Group 1: PD start <7 days ($n = 344$) Group 2: 8–14 days ($n = 176$) Group 3: 14 days ($n = 176$)	Catheter dysfunction Peritonitis Technique survival Patient outcomes (death, transfer to HD)	Mechanical complications higher in G1 (8.4%) vs. G3 (1.7%) No difference in prevalence of catheter dysfunction, technique failure or peritonitis between the three groups
See et al. [31]	Matched case control study	Urgent-start PD ($n = 26$) vs. conventional-start PD ($n = 78$)	Early complications Peritonitis rates Long-term technique survival	Urgent-start PD had increased leaks post catheter insertion (12% vs. 1%) and more frequent catheter migration post commencement of PD (12% vs. 1%) No differences in infections Long-term technique and peritonitis-free survival was the same
Ranganathan et al. [29]	Randomized control trial	Group 1: PD start at 1 week post catheter insertion ($n = 39$) Group 2: at 2 weeks ($n = 42$) Group 3: at 4 weeks ($n = 41$)	Catheter leaks	Catheter leaks: • Group 1: 28.2% vs. Group 2: 9.5%, Group 3 2.4%

PD, peritoneal dialysis; PTH, parathyroid hormone.

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Table 49.4a Summary of findings: urgent-start peritoneal dialysis versus conventional-start peritoneal dialysis (randomized controlled trials).

Urgent start peritoneal dialysis versus conventional-start peritoneal dialysis for people with chronic kidney disease						
	Anticipated absolute effects[a] (95% CI)					
Outcomes	**Risk with conventional-start PD**	**Risk with urgent-start PD**	**Relative effect (95% CI)**	**No. of participants (studies)**	**Quality of the evidence (GRADE)**	**Conclusions**
Dialysate leak	72 per 1000	**282 per 1000** (113–707)	**RR 3.90** (1.56–9.78)	122 (1 study)	⊕⊕⊖⊖ LOW	Urgent start PD may increase dialysate leak
Catheter blockage	–	–	–	No studies	Absent	
Catheter malposition	–	–	–	No studies	Absent	
Exit-site infection	–	–	–	No studies	Absent	
Peritonitis	–	–	–	No studies	Absent	
Catheter readjustment	–	–	–	No studies	Absent	
Technique survival	892 per 1000	**972 per 1000** (892–1000)	**RR 1.09** (1.00–1.20)	122 (1 study)	⊕⊖⊖⊖ VERY LOW	It is uncertain whether urgent start PD increases technique survival

CI, confidence interval; PD, peritoneal dialysis; RR, risk ratio.
GRADE Working Group grades of evidence: High: Further research is very unlikely to change our confidence in the estimate of effect. Moderate: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low: We are very uncertain about the estimate.
[a] **The risk in the urgent-start PD group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

received urgent-start PD were significantly more likely to be referred late to the nephrology service, defined as requiring to commence dialysis within 3 months of first nephrology review (73% vs. 1%, $P < 0.001$). The two groups were otherwise well matched for their demographic and clinical characteristics. The risk of complications within the first 4 weeks after catheter insertion was generally comparable between groups (e.g. catheter blockage, migration, exit-site infection, or peritonitis), other than a statistically significant increase in the risk of peri-catheter leak in the urgent-start PD group (12% vs. 1%, $P = 0.047$). Similarly, the risk of catheter migration was significantly higher in the urgent-start PD patients (12% vs. 1%, $P = 0.047$) within the first 4 weeks after PD commencement [31]. The peritonitis-free and technique survivals were comparable between the two groups in multivariable analyses adjusted for obesity and late referral status (peritonitis-free survival: adjusted hazard ratio [HR] 1.05, 95% confidence interval [CI] 0.25–4.37, $P = 0.95$; technique survival: adjusted HR 0.78, 95% CI 0.18–3.32, $P = 0.74$) [31]. Similar results, with an increase in the risk of early mechanical complications without impact on infection or technique survival, have been reported in other groups, including by Povlsen and Ivarsen, who were the early pioneers of urgent-start PD (28.9% vs. 7.7% in the first 3 months after PD commencement) [28]. A Canadian group also reported a higher incidence of catheter leaks (10%) in urgent-start PD patients, although all of the cases were successfully managed conservatively with lower dwell volumes [42]. Furthermore, at 24 months, 80% of patients were still performing PD, with only two patients switching to HD and the other 13.3% receiving transplantation [42]. Although there have been concerns about an increase in the risk of complications with higher initial fill volumes, studies have not been able to demonstrate this to date [57] and direct comparisons across literature have not been possible due to differences in the timing of PD initiation, approaches to PD catheter insertion, and PD modality [28, 30, 46, 51].

There are limited studies comparing the outcomes among different PD modalities within an urgent-start PD program. Liu et al. compared the early complications and overall efficacy among three different PD modalities: incremental CAPD, APD, and APD followed by CAPD. All

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Table 49.4b Summary of Findings: urgent-start peritoneal dialysis compared with conventional-start peritoneal dialysis for people with chronic kidney disease (non-Randomized Controlled Trials)

	Anticipated absolute effects[a] (95% CI)					
Outcomes	**Risk with conventional-start PD**	**Risk with urgent-start PD**	**Relative effect (95% CI)**	**No. of participants (studies)**	**Quality of the evidence (GRADE)**	**Conclusions**
Dialysate leak (cohort studies)	9 per 1000	**18 per 1000** (7–47)	**RR 2.06** (0.80–5.28)	1322 (7 studies)	⊕⊖⊖⊖ Very low	It is uncertain whether urgent-start PD increases dialysate leak
Dialysate leak (case-control studies)	10 per 1000	**73 per 1000** (12–425)	**RR 7.41** (1.27–43.36)	160 (2 studies)	⊕⊖⊖⊖ Very low	
Catheter blockage (cohort studies)	8 per 1000	**11 per 1000** (3–37)	**RR 1.33** (0.40–4.43)	1214 (4 studies)	⊕⊖⊖⊖ Very low	It is uncertain whether urgent-start PD increases catheter blockage
Catheter blockage (case-control studies)	39 per 1000	**74 per 1000** (23–240)	**RR 1.89** (0.58–6.13)	160 (2 studies)	⊕⊖⊖⊖ Very low	
Catheter malposition (cohort studies)	28 per 1000	**45 per 1000** (22–93)	**RR 1.63** (0.80–3.32)	1353 (6 studies)	⊕⊖⊖⊖ Very low	It is uncertain whether urgent-start PD increases catheter malposition
Catheter malposition (case-control studies)	38 per 1000	**115 per 1000** (25–537)	**RR 3.00** (0.64–13.96)	104 (1 study)	⊕⊖⊖⊖ Very low	
Exit-site infection (cohort studies)	11 per 1000	**15 per 1000** (3–93)	**RR 1.43** (0.24–8.61)	337 (2 studies)	⊕⊖⊖⊖ Very low	It is uncertain whether urgent-start PD increases exit-site infection
Exit-site infection (case-control studies)	128 per 1000	**154 per 1000** (53–449)	**RR 1.20** (0.41–3.50)	104 (1 study)	⊕⊖⊖⊖ Very low	
Peritonitis (cohort studies)	107 per 1000	**107 per 1000** (73–157)	**RR 1.00** (0.68–1.46)	1497 (7 studies)	⊕⊖⊖⊖ Very low	It is uncertain whether urgent-start PD increases peritonitis
Peritonitis (case-control studies)	284 per 1000	**310 per 1000** (34–1000)	**RR 1.09** (0.12–9.51)	160 (2 studies)	⊕⊖⊖⊖ Very low	
Catheter readjustment (cohort studies)	20 per 1000	**25 per 1000** (8–78)	**RR 1.27** (0.40–4.02)	739 (2 studies)	⊕⊖⊖⊖ Very low	It is uncertain whether urgent-start PD increases catheter readjustment
Technique survival (cohort studies)	757 per 1000	**681 per 1000** (575–810)	**RR 0.90** (0.76–1.07)	1668 (8 studies)	⊕⊖⊖⊖ Very low	It is uncertain whether urgent-start PD decreases technique survival
Technique survival (case-control studies)	627 per 1000	**577 per 1000** (496–665)	**RR 0.92** (0.79–1.06)	160 (2 studies)	⊕⊖⊖⊖ Very low	

CI, confidence interval; PD, peritoneal dialysis; RR, risk ratio.
GRADE Working Group grades of evidence: High: Further research is very unlikely to change our confidence in the estimate of effect. Moderate: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low: We are very uncertain about the estimate.
[a] **The risk in the urgent-start PD group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

patients were started on PD 1–3 days post-catheterization, but each group received different fill volumes without specific reference to their body size (650–1500 ml in the APD/APD-CAPD group and 500–1500 ml in the CAPD group). There was no difference amongst the groups in the risk of mechanical or infective complications within 1 month after PD commencement [56].

Urgent-start PD vs. Urgent-start HD

There have been studies that have evaluated outcomes in urgent-start PD versus unplanned HD which have shown that urgent-start PD was comparable to HD with respect to safety outcomes (Tables 49.5 and 49.6) [34, 35, 45, 51]. Jin et al. published a study in 2016 comparing the short-term

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Table 49.5 Urgent-start PD versus urgent-start HD.

Study	Design	Study population	Endpoint	Outcome (HD vs. PD)
Lobbedez et al. [35]	Prospective, observational	Unplanned HD ($n=26$) vs. urgent-start PD ($n=34$)	Hospitalizations and patient survival at 1 year Survival at 1 year	Mortality: 21.2% vs. 17.1% Hospitalizations: 24 ± 28 vs. 30 ± 33
Koch et al. [34]	Observational, cohort study	Unplanned HD ($n=57$) vs. urgent-start PD ($n=66$)	Mortality rates Risk of bacteremia Hospitalizations	Bacteremia within first month of dialysis: 21.1% vs. 3% Mortality: 42.1% vs. 30.3%
Ghaffari et al. [61]	Prospective cohort study	Unplanned HD ($n=78$) vs. urgent-start PD ($n=46$)	Hospitalizations, technique survival, catheter-related bacteremia	Catheter-related bacteremia: 4.3-fold higher adjusted rate in HD group Hospitalization: 1.43-fold higher adjusted rate in HD group Technique survival (6 month): 90% vs. 98%
Jin et al. [51]	Nonmatched, retrospective observational study	Unplanned HD ($n=82$) vs. urgent-start PD ($n=96$)	Dialysis-related complications, bacteremia, and patient survival at 30 days	Dialysis-related complications: 24.4% vs. 5.2% All HD patients with complications required catheter reinsertion Bacteremia: 13.4% vs. 3.1% Mortality: 1.6% vs. 2.3%
Jin et al. [45]	Retrospective, observational	Urgent-start HD ($n=41$) vs. urgent-start PD ($n=53$)	Dialysis-related complications Survival rates at 6, 12, 24, and 36 months	Dialysis-related complications: 30 days; 24.4% vs. 5.7% Survival rates: 6 months 94.6% vs. 92.3%, 12 months 81.3% vs. 82.4%, 36 months 60.6% vs. 69.5%

complications and survival rates between HD and PD patients requiring dialysis urgently. It was a retrospective, observational study involving 96 PD patients and 82 unmatched HD patients. Patients in the PD group had more cardiovascular disease (21.9% vs. 9.8%) and were less likely to suffer from heart failure (30.2% vs. 48.8%). However, there were no significant differences in age (PD group 55.2 ± 17.9 vs. HD group 51.2 ± 20.0), gender (males PD 58.3% vs. HD 53.7%) or prevalence of diabetes mellitus (32.3% vs. 24.4%) or hypertension (72.9% vs. 73.2%) between the groups. This study observed that, at 30 days, the rate of dialysis-related complications was much higher among HD patients than PD patients (24.4% vs. 5.2%, $P < 0.001$) [51]. For example, all of the 20 HD patients with dialysis-related complications required re-insertion of a CVC in contrast to only one PD patient who required PD catheter re-insertion. Furthermore, there was a higher incidence of bacteremia within the urgent-start HD group (13.4% vs. 3.1%). The survival rates were comparable in the two groups with actuarial patient survival at 12 months being 93% for HD and 92.1% for PD patients after 1 month of follow up [51]. Two single-center studies in France [35] and Germany [34] comparing unplanned PD and unplanned HD also showed similar mortality rates between the two groups. Koch et al. reported similar results to Jin et al., showing that patients started on unplanned HD had higher rates of bacteremia during the first 6 months of initiation dialysis (2.1% vs. 3%, $P < 0.01$) in the setting of using CVCs as initial vascular access [34]. These results were echoed in a prospective cohort study, which reported urgent dialysis through a CVC was associated with a 43% increase in hospitalizations compared with urgent-start PD, and the rate of catheter related bacteremia was 4.3-fold higher [61]. Overall, all of the studies comparing urgent-start PD and HD have observed increased rates of bacteremia in the setting of CVC use, with a higher burden of hospitalizations and need for catheter re-insertion.

Health Economics

There are also significant cost savings that can be seen in an urgent-start PD program in comparison to urgent-start HD. In 2014, Liu et al. performed an economic evaluation and found that the cost per patient over the first 3 months of urgent-start PD was $16 398. Comparatively, the estimated cost of urgent-start HD was $19 352 per patient for the first 90 days, showing that urgent-start PD may be a more cost-effective program [26].

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Table 49.6 Summary of findings: urgent-start peritoneal dialysis versus urgent-start haemodialysis (hemodialysis initiated with a catheter)

Outcomes	Anticipated absolute effects[a] (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Conclusions
	Risk with urgent-start HD	Risk with urgent-start PD				
Bacteremia	**151 per 1000**	**20 per 1000** (6–62)	**RR 0.13** (0.04–0.41)	301 (2 studies)	⊕⊕⊖⊖ Low	Urgent-start PD may reduce risk of bacteremia compared with urgent-start HD
Peritonitis	**7 per 1000**	**13 per 1000** (2–98)	**RR 1.78** (0.23–13.62)	301 (2 studies)	⊕⊖⊖⊖ Very low	It is uncertain whether urgent-start PD increases peritonitis risk compared with urgent-start HD
Exit site or tunnel infection	**18 per 1000**	**54 per 1000** (6–198)	**RR 3.99** (1.32–12.05)	419 (1 study)	⊕⊖⊖⊖ Very low	It is uncertain whether urgent-start PD increases risk of exit-site infection compared with urgent-start HD
Catheter malfunction	**151 per 1000**	**39 per 1000** (11–137)	**RR 0.26** (0.07–0.91)	597 (2 studies)	⊕⊖⊖⊖ Very low	It is uncertain whether urgent-start PD reduces catheter malfunction compared with urgent-start HD
Catheter readjustment	**373 per 1000**	**48 per 1000** (0–1000)	**RR 0.13** (0.00–18.61)	225 (2 studies)	⊕⊖⊖⊖ Very low	It is uncertain whether urgent-start PD reduces catheter readjustment compared with urgent-start HD
Technique survival	**526 per 1000**	**621 per 1000** (458–847)	**RR 1.18** (0.87–1.61)	123 (1 studies)	⊕⊖⊖⊖ Very low	It is uncertain whether urgent-start PD increases technique survival compared with urgent-start HD
Death (all-cause)	**204 per 1000**	**139 per 1000** (90–218)	**RR 0.68** (0.44–1.07)	820 (5 studies)	⊕⊕⊖⊖ Very low	It is uncertain whether urgent-start PD increases death (all-cause) compared with urgent-start HD

CI, confidence interval; HD, hemodialysis; PD, peritoneal dialysis; RR, risk ratio.
GRADE Working Group grades of evidence. High: Further research is very unlikely to change our confidence in the estimate of effect. Moderate: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low: We are very uncertain about the estimate.
[a] **The risk in the urgent-start PD group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

Conclusion

There is a growing burden of patients with end-stage kidney disease worldwide, with increasing numbers of patients commencing on renal replacement therapy [62]. A significant factor contributing to this burden is the number of patients initiating renal replacement therapy with a lack of established dialysis access. Urgent-start PD is emerging as a potentially safe and feasible solution to mitigate the need for CVC-facilitated HD in this population [62, 63]. There have been reports of an increase in the burden of early mechanical complications, particularly peri-catheter leaks, but these have often been managed successfully using conservative measures. However, it should be noted that the quality of reported evidence is restricted to often single-center, retrospective observational studies at risk of indication bias and residual confounding.

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Peritoneal Dialysis Catheter Insertion

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Introduction

Responsive and high-quality peritoneal dialysis (PD) access is an essential requirement for successful PD. For a PD catheter to work it requires the delivery of flow rates of up to 300 ml/min with the higher requirements being when automated PD is performed using a machine than for manual continuous ambulatory peritoneal dialysis (CAPD) using gravity to facilitate the drain [1]. If the flow rate cannot be delivered the consequences vary from troublesome machine alarms to extended treatment times and the inability to deliver the therapy. PD catheter insertion has a major impact on the uptake of the therapy for two important reasons. Poorly responsive access pathways delay and therefore inhibit access to PD, and poor catheter function increases early technique failure [2]. Mechanical causes of technique failure are a particular problem early in the course of PD, and poor catheter function can prevent patients from getting their chosen dialysis modality. Catheter dysfunction may be difficult to identify and can be misdiagnosed as impaired ultrafiltration.

Epidemiology

The evidence to support one insertion technique over another is not robust and the characteristics of the local kidney failure service and healthcare system are key factors in determining the approaches that are used. Although inserting PD catheters is a simple concept the reality is that there is considerable variation in primary catheter function and complication rates between centers within and between countries. For example, 1-year catheter survival in from the UK Renal Registry varies widely, with some centers reporting no catheter failures compared with others where the rate was greater than 40%; the median rate was 13% having fallen from 20% in previous reports [3]. The Brazilian Peritoneal Dialysis multicenter study identified comparable outcomes between surgical PD catheter insertions and those placed by interventional nephrologists. They reported mechanical complication rates of 10.5% and peritonitis rates of 10.2% by 3 months post insertion but were higher in those centers where the number of catheter insertions was low (<5), suggesting that operator experience may be more important than the actual insertion technique [4, 5].

Systematic reviews have not identified better outcomes of PD catheters placed using the percutaneous method compared with surgical insertion [6, 7] and gave inconsistent conclusions comparing open surgical to laparoscopic surgical insertion [8, 9]. A potential advantage of laparoscopy is that advanced techniques can be employed at the time of insertion to optimize catheter function, including omentopexy and adhesiolysis. There are no randomized controlled trials that examine this approach, but a systematic review of cohort studies reported an advantage for advanced laparoscopic interventions consisting of rectus sheath tunneling and adjunctive procedures compared with basic laparoscopy, which is used only to verify the catheter position [10]. This may have particular value in the evaluation or replacement of catheters that did not work well at the first insertion. Of course, one of the difficulties in evaluating advanced technique evidence is that studies may use some, but not all, of the techniques and this generates considerable heterogeneity.

International variation in PD access will be reported from the Peritoneal Dialysis Outcomes and Practice

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Patterns Study (PDOPPS) [11]. Early data indicates that the open surgical approach is favored in Japan, laparoscopy in the United State, with percutaneous techniques being available in about 50% of Australian, UK, and Canadian centers (Wilkie M et al., [51]. Abstract to European Renal Association – European Dialysis and Transplant Association meeting June 2017). Local factors influence the catheter insertion process, such as the availability of surgical staff and the responsiveness of the service, which impacts on whether PD can be used to treat late-presenting patients. Many centers rely on a single surgical approach for all patients, whereas others practice a combination of medical or percutaneous and surgical insertion techniques stratified according to individual requirements [3].

The Catheter Insertion Pathway

The decision regarding the most appropriate PD catheter insertion technique is influenced by a range of factors. For example, those who present unexpectedly to the renal service, or have a rapid decline in renal function, require a responsive PD catheter insertion pathway if they are to be able to successfully commence PD. There is some evidence to suggest that percutaneous insertion may potentially result in a more responsive service [12], with particular advantages for patients presenting late with advanced chronic kidney disease and in need of urgent start PD [13]. This may be because it is logistically easier to organize a percutaneous compared to a surgical insertion that may be at more risk of delay due to such factors as availability of operating theater space and the requirement for preoperative anesthetic assessment. Percutaneous insertion by nephrologists was associated with increased uptake of PD in a population-based retrospective cohort study using administrative health data from Ontario, Canada [14]. In the 2016 UK Renal Registry reported incident use of PD was 25.9% at centers that placed nonsurgical PD catheters compared with 21% in centers that used only used surgical placement [3].

Success of PD catheter insertion is impacted by a multiplicity of factors, including patient comorbidities, aspects of patient preparation including education, logistics of catheter insertion (e.g. access to theater space, bed availability, and responsiveness of the pathway), post-catheter care, the approaches to catheter use, and patient training. These practices vary considerably between patients and centers, and although there are recommendations with respect to components of the pathway, robust evidence is lacking [15]. Certain characteristics define those who are suitable for percutaneous insertion, including the absence of significant central obesity and of major abdominal scars. Significant lower abdominal surgery will affect the catheter insertion approach since the likelihood of success may be affected by the presence of residual adhesions. Upper abdominal surgery is generally not likely to interfere with the placement or function of the PD catheter. With the surgical insertion technique the majority of patients will receive a general or spinal anesthetic and although this may be performed as a day-case procedure, patients receiving general anesthesia may well require a short inpatient hospital stay and commonly a preoperative assessment.

An important aspect of catheter insertion is that the care pathway extends beyond the actual catheter insertion and includes appropriate patient preparation, with many centers employing the practices of decolonization of *Staphylococcus aureus*, antiseptic skin washes, bowel preparation, appropriate catheter selection, and exit site planning. The location for the catheter exit site should be determined in discussion with the patient, giving consideration to body shape and size, as well as clothing and sleeping habits. If the exit site is placed below the abdominal fold then it is more difficult for the patient to care for the site themselves, and if it is placed at the belt line abrasion will prevent healing and rapidly precipitate infection, risking catheter survival. Appropriate catheter length can be determined using an approach that considers patient size carefully to ensure that the catheter tip is placed in the pelvis, but not so long that it causes contact pain or kinks. There are approaches that can be used here, including the use of a template to guide catheter size or adjustments to the exit site position so that it is optimally placed [16]. There is no evidence for the routine use of plain abdominal X-rays to locate the catheter position post insertion or at intervals as part of follow-up.

Insertion Techniques

The techniques that are commonly used for PD catheter insertion include surgical placement by dissection [17], blind percutaneous placement using a guidewire (Seldinger technique) [18], percutaneous insertion guided by ultrasound [19] and fluoroscopy [20], as well as peritoneoscopic [21] and laparoscopic insertion techniques [22, 23]. Modifications of PD catheter insertion include embedding the external end of the catheter in a subcutaneous pouch until required [24] and the use of extended (upper abdominal and presternal) catheters [25, 26]. It is beyond the scope of this chapter to describe the techniques in detail. However, it is important to note that many studies include variations of described techniques that can significantly impact on outcome. For example, suture of the catheter tip to the bladder or uterus is commonly used to reduce tip migration [27] but may be associated with rare complications [28]. The laparoscopic technique commonly includes the addition of one or several additional procedures (as described below).

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Interventions

The literature is full of single-center cohort studies, commonly retrospective, that claim advantage for one insertion technique over another or a "new" variant of a technique or catheter. Blinding of the operator to the insertion technique is not possible and where cohort studies compare catheter insertion techniques it is difficult to be clear on the decision making that led to the selection of a particular technique for a particular patient. For this chapter we present evidence from randomized controlled trials involving adults and children, and have referred to cohort studies for descriptive purposes only. Data extraction was carried out independently by two authors (VB/MEW) using standard data extraction forms. The same authors assessed risk of bias using the appropriate assessment tool [29] and the quality of the evidence using the GRADE system [30]. JF and BMS reviewed evidence independently and adjudicated in the ensuing discussions. Outcomes include catheter survival, technique failure, surgical complications (hernias, leaks, and hemorrhage), infection (including peritonitis, exit site, and tunnel infections), patient-reported outcomes if reported (e.g. catheter related pain), catheter obstruction, and tip migration. The data we present will have similarities to a Cochrane review that is in preparation [31].

Laparoscopic Versus Open Surgical PD Catheter Insertion

Four studies randomized a total of 272 patients to receive either laparoscopic or open surgical PD catheter insertion (Table 50.1) [32–35]. Outcomes reported included peritonitis rates, exit site infection, post-operative dialysate leak, all-cause catheter removal, and operative time. Catheter tip migration, mechanical catheter failure, mean catheter survival, post-operative bleeding, and exit site infection were reported by some but not all studies. One- and 2-year catheter survival was only available as raw data for one of the four studies examined [35] since although survival analysis was undertaken in two of the studies [33, 34], the data were not available in a form to accurately determine 1- and 2-year catheter survival.

Insertion technique had no evidence of impact on catheter removal, peritonitis, or exit site infection rates following PD catheter insertion. All four studies collected data on the number of dialysate leaks post-operatively. The resulting meta-analysis showed a high level of heterogeneity.

Key differences existed between these studies, since the Tsimoyiannis study compared basic laparoscopy (plus suture fixation of catheter to the bladder or uterus) with open insertion [33] and the Van Lannen (CAPD 1 trial) included adhesiolysis where necessary and pre-peritoneal tunneling for all cases [35]. These two studies included adhesiolysis, whereas the Wright study did not include additional techniques [34]. The catheter fixation approach used in the Tsimoyiannis study clearly represented a major technique variation and we therefore conducted a sensitivity analysis and excluded that study [33]. Repeat meta-analysis improved heterogeneity significantly but still did not show any evidence for different outcomes related to open surgical PD catheter insertion over laparoscopic insertion (relative risk [RR] 2.31, 95% confidence interval [CI] 0.31– 17.32, I^2 0%). Three studies reported catheter tip migration [32, 33, 35] including 212 patients with meta-analysis showing no difference between the techniques (RR 0.31, 95% CI 0.07–1.48, $P = 0.114$, I^2 40%). The risk of bias was moderate in all studies (mainly due to inability to blind the operator/assessors). The CAPD 1 trial [35] used different terminology ("malposition within the bowels") and there was no difference in this parameter between the groups.

We present a summary of findings table (Table 50.1) for the following outcomes: all-cause PD catheter removal, peritonitis, exit site infection, post-operative dialysate leak, and catheter tip migration. These outcomes were reported with either three or four studies.

Peritoneoscopic Versus Open Surgical PD Catheter

The peritoneoscope allows visualization of the peritoneal cavity, but does not permit manipulation of peritoneal cavity contents and cannot be classed as a variation of laparoscopy. It is, however, distinct from percutaneous technique, which is a blind technique.

A single study examined peritoneoscopic insertion versus open surgical insertion reporting superior catheter survival for the former [36]. PD catheter survival was 77.5% vs. 62.5% ($P = 0.02$) at 12 months, 63% vs. 41.4% ($P = 0.01$) at 24 months, and 51.3% vs. 36% ($P = 0.04$) at 36 months in the peritoneoscopic and the open surgical PD catheter groups, respectively. Leaks and peritonitis were more common in the open surgical group, indeed early peritonitis (less than 2 weeks following surgery) occurred in 12.5% of the open surgical group and 2.6% of the peritoneoscopic insertion group. The level of early peritonitis reported in the open surgical group was much higher than that described as acceptable in international guidelines [15]. Equally, the 1-year catheter survival in the open surgical group was lower than that in most centers reporting to the UK Renal Registry [3]. We downgraded the evidence from this study for catheter survival on the basis of inconsistency

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Table 50.1 Summary of findings.

Laparoscopic compared to open surgical PD catheter insertion for improving catheter function and clinical outcomes in peritoneal dialysis patients

Patient or population: Improving catheter function and clinical outcomes in peritoneal dialysis patients
Setting:
Intervention: Laparoscopic
Comparison: Open surgical PD catheter insertion

	Anticipated absolute effects[a] (95% CI)					
Outcomes	**Risk with open surgical PD catheter insertion**	**Risk with laparoscopic**	**Relative effect (95% CI)**	**No. of participants (studies)**	**Certainty of the evidence (GRADE)**	**Comments**
Peritonitis	250 per 1000	**280 per 1000** (173–455)	**RR 1.12** (0.69–1.82)	167 (three RCTs (randomized controlled trial))	⊕⊕⊕◯ MODERATE[b]	Evidence downgraded due to risk of bias consequent on absence of blinding.
All cause PD catheter removal	297 per 1000	**341 per 1000** (238–487)	**RR 1.15** (0.80–1.64)	257 (four RCTs)	⊕⊕⊕◯ MODERATE[b]	Evidence downgraded due to risk of bias consequent on absence of blinding.
Exit site infection	139 per 1000	**153 per 1000** (82–286)	**RR 1.10** (0.59–2.06)	212 (three RCTs)	⊕⊕⊕◯ MODERATE[b]	Evidence downgraded due to risk of bias consequent on absence of blinding.
Dialysate leak	70 per 1000	**63 per 1000** (7–568)	**RR 0.90** (0.10–8.08)	257 (four RCTs)	⊕⊕⊕◯ MODERATE[b]	No significant difference in the rate of dialysate leak was demonstrated.
Dialysate leak, excluding Tsimoyiannis	10 per 1000	**22 per 1000** (4–123)	**RR 2.36** (0.43–12.92)	209(three RCTs)	⊕⊕⊕◯ MODERATE[b]	Due to high heterogeneity (56%), Tsimoyannis study excluded. There was a significant variation in the type of laparoscopic procedure performed in this study. On exclusion, heterogeneity reduced to 0%. No significant difference was demonstrated.
Catheter tip migration	135 per 1000	**42 per 1000** (9–199)	**RR 0.31** (0.07–1.48)	212 (three RCTs)	⊕⊕⊕◯ MODERATE[b]	Evidence downgraded due to risk of bias consequent on absence of blinding.

CI, confidence interval; RR, risk ratio.
GRADE Working Group grades of evidence. High certainty: We are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.
[a] **The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
[b] High risk of bias due to inability to blind either operators or assessors.
Sources: Jwo et al. [32], Tsimoyiannis et al. [33], and Wright et al. [34].

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to moderate, i.e. the infection rate in the control group was higher than expected and this was likely to impact on the catheter survival rate. The results of this study should be evaluated in a further randomized controlled trial.

A second study used a cystoscope (usually used for examining the bladder) to visualize the peritoneal cavity [37]. This study randomized 29 patients to either open surgical PD catheter insertion or insertion assisted with direct vision using the cystoscope. The study was too small to be able to draw robust conclusions and did not add materially to the evidence base. The complication rate in the cystoscope group was very low at 1 out of 14 and in the open surgical group was 12 of 15 cases. Here we felt there was inconsistency of results and therefore lacked the confidence to perform a meta-analysis of these two trials.

Percutaneous Versus Open Surgical PD Catheter Insertion

Two studies looked at the use of a percutaneous method to insert PD catheters and compared this to standard open surgical insertion. One study looked at a pediatric population below the age of 15 years [38] and the other included adult patients only [39]. Both studies followed patients up for 2 months only.

The adult study was conducted in Iran, recruiting 64 patients, although three were excluded by the authors because of cardiac death [39]. One catheter in the percutaneous group and four catheters in the open surgical group developed outflow failure within 2 months. Two patients in each group developed catheter tip migration. Five patients developed catheter malfunction due to omental wrapping (four in the surgical group and one in the percutaneous group) and omentectomy was carried out for these five patients. Hemoperitoneum was not clearly defined in the paper, but was reported in four patients in the surgical group but only one in the percutaneous group. Exclusion criteria with respect to previous surgery were not reported. The study concluded that percutaneous insertion has fewer complications and is quicker than the open surgical approach.

The second was a pediatric study of 35 patients (mean age 6.7 years) from the same Iranian hospital and recruited patients for 1 year [38]. Reported early complications were two exit site infections, post-operative bleeding, and dialysate leak. Omentectomy was performed in patients with catheter dysfunction but the study did not report any other survival data. Catheter malposition was seen in 17.6% of the surgical group and 5.5% of the percutaneous group, but the study sample was small and no *P* value was reported.

Both studies reported duration of hospital stay and operative time. There were no differences in these times between the two studies although it is not clear whether the operators were the same in the two studies. The operative time in the percutaneous insertion group was significantly lower than in the open surgical group in both studies (approximately 10 minutes). We do not present a meta-analysis of these two studies because of the age group difference, but there are no obvious differences in mechanical catheter failure. We have downgraded the evidence from these studies on the basis of the short follow-up period, but they provide moderate evidence of similar outcomes between percutaneous and open surgical techniques.

Radiological Versus Laparoscopic Catheter Insertion

A single noninferiority randomized controlled trial compared radiologically guided fluoroscopic with laparoscopic PD catheter insertion, excluding patients who were obese or who had previous abdominal surgery [40]. This study also examined the economic impact of each type of PD catheter insertion, particularly as the type of anesthetic can impact on the length of hospital stay for each procedure and laparoscopy requires a general anesthetic whilst percutaneous procedures that are guided fluoroscopically can be done with local anesthesia. Although there was no difference in catheter survival between the groups, complication-free catheter survival was significantly higher at 42.5% (95% CI 29.3–55) in the radiological group compared with 18.1% (95% CI 8.9–29.8) in the laparoscopic group. Complications in the laparoscopic group included infection (peritonitis and exit site), peritoneal dialysate leaks, and umbilical hernia. The radiological percutaneous approach was associated with benefits with respect to pain scores, procedure time, and direct hospital costs. This study was well conducted and provides evidence that the fluoroscopic method of PD catheter insertion was not inferior to laparoscopic insertion.

Laparoscopy with Adjunctive Techniques

The advanced laparoscopic insertion technique, introduced by Crabtree et al., involves placement of the PD catheter under laparoscopic visualization, with additional components such as rectus sheath tunneling, omentopexy, adhesiolysis, excision of appendix epiploica (epiploectomy), salpingectomy, and colopexy [23, 41]. This approach has only been examined in cohort studies, both retrospective and prospective. A meta-analysis of six observational studies [23, 42–46] compared the outcome of advanced laparoscopy with open insertion and reported reduced risk of catheter obstruction (odds ratio [OR] 0.14, CI 0.03–0.63), migration (OR 0.12, 95% CI 0.6–0.26), peri-catheter leak

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(OR 0.27, 95% CI 0.11–0.64), and hernia (OR 0.29, 95% CI 0.09–0.94), as well as improved 1-year (OR 0.52, 95% CI 0.08–0.97) and 2-year catheter survivals (OR 0.50, 95% CI 0.28–0.92). There was no difference in infectious complications between the two groups [10]. Three studies compared the outcome of basic and advanced laparoscopy [23, 43, 47]. In meta-analysis, catheter obstruction (OR 0.11, 95% CI 0.05–0.21) and migration (OR 0.07, 95% CI 0.01–0.51) were significantly lower in the advanced laparoscopic group, whereas peri-catheter leak, infectious complications, and catheter survival were similar in both groups [10]. The quality of this evidence is low on the basis of the lack of randomization and blinding. The single randomized controlled trial that compared laparoscopy involving preperitoneal tunneling compared with open surgical insertion did not demonstrate a difference in catheter survival and we have included that study in the meta-analysis of laparoscopic versus surgical insertion (Table 50.1) [35].

Other Approaches

A prospective randomized study of standard open surgical PD catheter insertion compared buried (embedded) to nonburied catheters in 60 participants in whom PD start was planned for at least 6 weeks after PD catheter insertion [48]. Catheter failure due to mechanical reasons was very low, with only one patient in the buried catheter group terminating PD for this reason. There was a nonsignificant trend to lower peritonitis rates in the buried group. The Kaplan–Meier curves produced were not sufficiently detailed to be able to extract numerical information. A limitation of this study was that the insertion technique differed slightly between the two centers that participated.

Omental wrapping is a cause of PD catheter dysfunction and can require catheter removal or replacement. Whilst not a direct comparison of insertion techniques, a prospective randomized study examined the role of intra-operative greater omental folding during PD catheter placement to determine impact on PD catheter function [49]. One difficulty of this study was that the decision regarding whether the greater omentum was of sufficient size to merit inclusion into the study had to be made by the surgeon intraoperatively. Omental folding had no impact on technique failure ($P = 0.32$), infection rates ($P = 0.74$) or other postoperative complications such as bleeding ($P = 0.35$) and dialysate leak ($P = 0.57$). However, there were significantly lower levels of PD catheter tip migration and irreversible PD catheter dysfunction ($P = 0.03$) in patients with omental folding ($P = 0.04$).

PD catheter fixation within the pelvis at the time of PD catheter insertion was examined in a single randomized controlled trial [27]. In this study 152 patients were randomized to a traditional open surgery group, a modified open surgery group or a modified open surgery with catheter fixation group. The surgical modification was to use a lower than usual implantation position 7 cm above the pubic symphysis and the catheter fixation was by means of a suture around the catheter 3 cm below the inner cuff. Complication rates were comparable between the two techniques, but catheter tip migration (with catheter malfunction) was lower in the group with catheter fixation ($P < 0.05$). Catheter survival at 1 year following catheter insertion was 84% in the traditional open surgical group, 96% in the modified open surgical group, and 100% in the catheter fixation group.

Quality Assurance of Catheter Insertion Pathways

The objective of access pathways is to provide safe and responsive PD access that works. Audit standards have been suggested in guidelines with little evidence to demonstrate their utility. Currently recommended outcome measures focus around 1-year catheter survival censored for death and transplantation. However, much more proximate measures of success would be beneficial. The key question for patients is whether the catheter worked at the time it was needed for the therapy that was preferred.

Complications that should be monitored include infection (exit site and peritonitis), catheter flow problems, leaks, catheter tip pain, hemorrhage (defined as sufficiently extensive to lead to blood transfusion), and perforation of a viscus. The last two from that list are extremely rare and although guidelines recommend that they are included in the post-insertion audit, the numbers are not sufficient to permit comparative audit. PD catheter dysfunction has been variously defined, perhaps a functional definition is most useful such as catheter function being sufficient to permit treatment with the patient's chosen modality (be that automated peritoneal dialysis [APD] or CAPD).

Guidelines have recommended delaying the use of the PD catheter for 2 weeks post catheter insertion to permit healing and reduce the likelihood of leaks, but this recommendation may have inhibited the use of urgent start PD [15]. PD catheters can be used immediately as long as appropriate measures are taken to reduce the risk of leaks, such as ensuring that the patient is supine while there is fluid in the peritoneal cavity during the first few days of use. A randomized controlled trial of early versus later start demonstrated increased complications in the early start group, but complication rates were higher than those reported from other centers where early start PD is used [50].

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Table 50.2 Treatment recommendations.

Treatment	Recommendation	Certainty of evidence	Strength of recommendation
Method of peritoneal dialysis catheter insertion	We do not suggest any specific PD catheter insertion technique for improving PD patient outcomes based on low to very low certainty of the evidence that choice of catheter insertion technique makes any difference to the outcomes of peritonitis, all-cause PD catheter removal, exit site infection, post-operative dialysate leak, incisional hernias catheter obstruction or catheter tip migration	Low to very low evidence	Weak

Conclusion and Recommendation

Evidence is not sufficient to recommend one PD catheter insertion technique over another therefore operators should continue to use techniques with which they are familiar (Table 50.2). We performed meta-analysis for four randomized controlled trials comparing laparoscopic versus open surgical insertion and did not find any significant advantages for one technique over another for the outcomes we considered. A weakness of our analysis is that the technique is defined only by the use of the laparoscope or not techniques that it is used for. There is the potential that combining laparoscopy with adjunctive techniques that can be performed during the procedure could reduce the risk of catheter migration or obstruction. This insertion technique may have particular value when individuals have had previous lower abdominal surgery or a first catheter that did not work. This has not been tested in randomized controlled trials (table 50.2).

A recommendation for a particular PD catheter insertion technique should take into consideration the characteristics of the patient, locally available expertise, and resources. For example, the use of local anesthesia for percutaneous insertion has the advantage that it can provide definitive access in individuals with significant comorbidities and for whom a general anesthetic may be contraindicated. We would therefore recommend that where possible centers aim to provide a combination of approaches that are stratified according to the needs of the individual. It is important that regular local audit is conducted of PD catheter outcomes and complication rates.

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Part 8

Supportive Care

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51

Overview of Kidney Supportive Care

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Defining Kidney Supportive Care

Kidney supportive care (KSC) is the integration of palliative care principles in the holistic, patient-centered management of chronic kidney disease (CKD). It has evolved out of the recognition that patients with CKD, particularly those with advanced CKD with or without dialysis, have high symptom burden and poor quality of life. Furthermore, there are increasing numbers of patients with end-stage kidney disease (ESKD) who are older, frail, and have multimorbidity and poor functional status, where treatment with dialysis may be of little or no benefit and potentially harmful (Table 51.1). While this is the group for whom KSC most often applies, patients with all stages of CKD require active and holistic management of their evolving care needs (see Table 51.2) and as such patients may benefit from KSC at any stage in their CKD trajectory.

The key elements of KSC include:

1) Active care aligning nephrology and palliative care, best provided by a multidisciplinary team that includes kidney and palliative care expertise from physicians, nurses, and allied health staff such as dieticians and social workers, underpinned by education, research, and quality assurance.
2) Meticulous and evidence-based symptom management in CKD.
3) Shared decision-making, with an emphasis on skilled communication, provision of information including prognosis, and informed decision-making regarding the initiation and withdrawal of dialysis or opting for conservative (nondialysis) kidney management (CKM).
4) Provision of active patient-centered care for patients with advanced CKD or ESKD, particularly those who are planning CKM, addressing physical, psychosocial, and spiritual needs.
5) Advance care planning.
6) Terminal/end-of-life care.

Rationale for the Development of a Kidney Supportive Care Model

Several key observations underpin the need for a KSC model. First, the mortality for ESKD remains high despite the availability of renal replacement therapy (RRT), particularly for those on dialysis. Second, CKD patients are increasingly older, with multimorbidity and the difficult decision of determining which patients may benefit from dialysis and actively supporting those who may not benefit becomes a core skill and imperative for nephrologists. Third, symptom burden is high for patients with CKD, especially for those with advanced CKD and ESKD, whether treated with dialysis or CKM. These symptoms are often under-recognized and untreated in routine nephrology practice.

Mortality in End-stage Kidney Disease

ESKD is associated with high mortality and although dialysis may prolong survival in selected patients, it does not restore normal life expectancy [15]. Mortality is particularly high among older patients commencing dialysis. Table 51.3 shows life-expectancy of ESKD patients in several Western countries with widespread availability of

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Table 51.1 Summary of the key components of kidney supportive care.

Component	Recommendation	Certainty of evidence	Strength of recommendation
Symptom management	We suggest regular symptom assessment using validated tools such as iPOS renal and ESAS-r : Renal	Low	Weak [1–4]
Shared decision-making	We encourage shared decision-making at key time points, including dialysis initiation and withdrawal, advance care planning, and pursuing CKM	Absent	Weak [5]
Prognostic information	We suggest clinician-led discussions of prognosis, as the majority of patients on dialysis would like this information	Low	Weak [6, 7]
	Furthermore, dialysis may not offer survival advantage to older patients with comorbidities and poor functional status	Low	Weak [8–11]
Advance care planning	We suggest advance care planning for patients with advanced CKD	Very low	Weak [5, 12]
Communication	We suggest nephrologists have proficiency in communication skills to lead serious illness conversations using communication tools	Absent	Weak [13, 14]

CKD, chronic kidney disease; CKM, conservative kidney management; ESAS-r:R, Edmonton Symptom Assessment System-Revised: Renal; iPOS, Integrated Palliative Care Outcome Scale.

Table 51.2 Components of kidney supportive care.

KSC		All CKD patients		
• Symptom management • Shared decision-making • Prognostic information • Medical CKD management • Advance care planning • End-of-life care, including dialysis withdrawal	→	Stage I–IV CKD	ESKD	
			Dialysis	CKM

CKD, chronic kidney disease; CKM, conservative kidney management; ESKD, end-stage kidney disease; KSC, kidney supportive care.

RRT [15, 16, 18]. Table 51.4 shows survival on dialysis in Australia, New Zealand, and Canada, with comparisons to common cancers in Australia [16, 20, 21].

Age and Comorbidities

Patients with ESKD are increasingly older with multimorbidity. In the United States, patients aged 75+ make up the largest group of incident dialysis patients, followed by those aged 65–74. Patients aged 65–74 remain the most prevalent group, likely due to higher mortality in the 75+ group, although data from the United States Renal Data System (USRDS) shows that those aged 75+ have formed the fastest growing group of prevalent dialysis patients in recent years. [22] Similarly, in Australia, between 2012 and 2016, the largest group of new dialysis patients were aged 75–84, followed by those aged 65–74 [23], although similar to the United States, patients aged 65–74 remained the most prevalent group [24].

In addition, comorbidities are common among ESKD patients, indicating that these patients are living with multiple serious chronic diseases. Australia and New Zealand Dialysis and Transplant Registry (ANZDATA) shows that between 2006 and 2016, the prevalence of type 2 diabetes is rising, both in Australia and New Zealand, approaching 40% by 2016 [24]. In Canada, Canadian Organ Replacement Register (CORR) shows that over 50% of incident dialysis patients in 2016 were diabetic [20].

Cardiovascular disease has remained more stable in Australia and New Zealand, with prevalence of coronary artery disease around 35% in Australia, lower in New Zealand [24]. USRDS data shows prevalence of any cardiovascular disease at over 70% for prevalent hemodialysis patients. The most common cardiovascular diseases include atherosclerotic heart disease, congestive heart failure, and peripheral vascular disease. In those aged 65 years or older, prevalence of atherosclerotic heart disease alone exceeds 50% [22].

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Table 51.3 Life expectancy on renal replacement therapy for older patients.

United States
Expected survival (years) of prevalent dialysis patients having attained a certain age, compared to general US population
Based on 2013 data [15]

Survival in years	Prevalent dialysis patients		General age-matched population	
Age group	Male	Female	Male	Female
40–44	11.0	10.4	36.4	40.3
45–49	9.2	8.9	31.9	35.6
50–54	7.9	7.8	27.7	31.1
55–59	6.6	6.6	23.7	26.8
60–64	5.5	5.7	19.8	22.6
65–69	4.5	4.8	16.2	18.5
70–74	3.8	4.0	12.8	14.7
75–79	3.2	3.5	9.8	11.3
80–84	2.6	2.9	7.1	8.4
85+	2.2	2.4	3.7	4.4

Australia and New Zealand
Median survival of incident dialysis patients by age, compared to general Australian population having attained a certain age
Based on 2017 ANZDATA [16]
Comparison with general population in Australia having attained a certain age

Survival in years	Incident dialysis patients		General population (2014–2016 in Australia) [17]		
Age group	Australia	New Zealand	Age	Male	Female
45–64	6.5	5.4	45	37.1	40.6
65–74	4.6	3.7	65	19.6	22.3
75–84	3.5	2.9			
85+	2.3	1.9	85	6.2	7.3

Median survival on dialysis is lower if patients have vascular disease and/or diabetes

United Kingdom
Median survival of incident RRT patients by age[a] compared to general population in UK at age 65
Based on 2015 data from UK Renal Registry [18]

Survival in years	Incident RRT patients	General population (2015–2017) [19]		
Age group		Age	Male	Female
55–64	6			
65–74	3.5	65	18.6	20.9
75+	2–2.5			

[a] Renal replacement therapy (RRT) includes both dialysis and transplantation.

Symptoms in End-stage Kidney Disease

Symptoms are prevalent in CKD, particularly across stages 3–5. Table 51.5 shows the most commonly reported symptoms in patients with CKD. More recent research has highlighted fatigue as the most common and distressing symptom, experienced in approximately 80% of patients with CKD or ESKD, regardless of whether they are treated with dialysis or CKM [4, 25]. Symptom assessment needs to be performed regularly and using validated tools.

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Table 51.4 Survival on dialysis compared with common cancers.

Age group	1 year	5 years
Australia: Incident dialysis patients 2007–2016 [16] % survival (95% CI)		
65–74	88 (87–89)	50 (48–51)
75–84	83 (82–84)	33 (32–35)
85+	72 (69–76)	20 (16–24)
New Zealand: Incident dialysis patients 2007–2016 [16] % survival (95% CI)		
65–74	87 (85–89)	38 (34–41)
75–84	81 (77–84)	20 (16–25)
85+	85 (65–94)	19 (6–39)
Canada: Incident dialysis patients 2007–2016 [20] % survival		
65–74	81.7	39.0
75+	73.4	25.7
Australia: Cancer patients 2009–2013 [21] 5-year survival		
Breast cancer (all)		90%
Breast cancer (aged 75+ at diagnosis)		79%
Colorectal cancer (all)		69%
Colorectal cancer (aged 75+ at diagnosis)		61%
Lung cancer (all)		16%
Lung cancer (aged 75+ at diagnosis)		10%

The Integrated Palliative Care Outcomes Scale (iPOS renal) [26] and Edmonton Symptom Assessment System-revised: Renal (ESAS-r:R) [27, 28] are such tools developed and used in research and in clinical practice [29–31]. Without the use of symptom tools, patients may be reluctant to disclose their symptoms to treating physicians. Studies have found that systematic questioning of symptoms yields many more symptoms than patients' self-reporting [5, 6]. Furthermore, this helps to direct the consultation toward more patient-centered goals and concerns that matter the most to patients.

Integration of Palliative Care

Palliative care is a discipline that focuses on improving the quality of life of patients and their families living with life-limiting illnesses through impeccable assessment and management of physical, psychosocial, and spiritual needs [7]. This can occur at any stage in the disease trajectory, alongside therapies that prolong life. The philosophy of palliative care can be applied to the management of patients with CKD to improve symptom burden, facilitate discussions regarding goals of care, offer better psychosocial and spiritual support, and prepare those patients and their families facing end-of-life issues. (Refer to Chapter 52 for a detailed discussion on the epidemiology and approach to symptoms in patients with CKD.)

Table 51.5 Prevalence of symptoms in chronic kidney disease.

Symptom	Prevalence	Evidence
Sleep disorders	60%	40 studies of 7391 patients
Pain	58%	>50 publications of 7500 CKD patients
Anorexia	56% (range 9–82%)	18 studies of 3122 patients
Nausea	46% (range 9–90%)	14 studies of 1774 patients
Uremic pruritus	41% (reported as severe in 24.5%)	24 studies of 19 226 dialysis patients
Constipation	40% (range 8–65%)	17 studies of 2001 patients
Vomiting	23% (range 11–68%)	12 studies of 1511 patients
Depression	22% in CKD stage 1–4 23% in dialysis patients	Palmer et al. [1]
Diarrhea	21% (8–33%)	10 studies of 921 patients
Restless legs syndrome	10–20% of long-term dialysis patients	Novak et al. [2]

Source: Adapted from Davison et al. [3].

Nonabandonment

The principle of nonabandonment can be defined as a longitudinal commitment from the physician both to care about patients and to jointly seek solutions to problems with patients throughout their illness, as an open-minded, caring, and knowledgeable partner [32]. It is a central principle in KSC in providing an engaged long-term relationship with patients and ensuring continuity of care regardless of their decision to commence or forego dialysis and other life-prolonging treatments. Several aspects of nonabandonment are particularly important for the physician to adopt in the KSC setting:

- Commitment to working with the patient through an unknown future without shying away from difficult decisions such as the appropriateness of dialysis and to continue to respond together to changing clinical situations.
- Willingness to be opened-minded about patients' values and goals and to share in patients' vulnerability and suffering in the context of a chronic and incurable illness.

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- Obligation to continue to care and advocate for patients through progressive disease to the end of life, accepting the limitations of medical therapies to prolong life or relieve suffering, and not deserting patients.

Models of Care

Based on the considerations relevant to this population, suggested components of a KSC team include some or all of:

- clinical nurse consultant specializing in KSC
- nephrologist
- palliative care physician
- trainee doctors and nurses
- nephrology and/or palliative care trainee
- social worker
- renal dietician
- renal pharmacist
- research assistant and data manager
- occupational therapist
- physiotherapist
- psychologist.

Models of care will depend largely on local needs and resources available, thus not all team members will be incorporated into one KSC service.

Integrated Model

The KSC model established at St. George Hospital in metropolitan Sydney, Australia integrates expertise from nephrology, palliative medicine, and a range of allied health disciplines to provide a service for patients and their families that is embedded within the existing kidney unit. The service is available to all patients with CKD, although the majority utilizing this service are older patients with advanced stages of CKD, about two thirds are pursuing a CKM pathway, and the remainder are undergoing dialysis or have advanced CKD with symptoms. All patients receive ongoing care from their treating nephrologist, including those with ESKD, regardless of their decision to pursue, withhold, or cease dialysis, adopting the principle of nonabandonment. The key elements of this model include:

- A dedicated KSC outpatient clinic, staffed by a palliative care physician, a nephrology advanced trainee, clinical nurse consultants, dietician, and social worker.
- Inpatient consultative service, led by the KSC nurse consultant.
- Regular and ad hoc phone and tele-health consultations for outpatients.
- Data collection for research and quality assurance purposes.
- Close liaison with treating nephrologists, dialysis staff, and local hospice and community palliative care services.
- Training and support for nephrology advanced trainees, and medical, nursing, and allied health staff from other kidney units.
- Regular meetings of the KSC team to ensure the service continues to develop, discuss difficult cases, and enhance research ideas.

Consultative Model

Embedding palliative care within a kidney unit allows for their regular and comprehensive involvement in providing a KSC service. However, this may not be practical or sustainable due to financial, logistic or resource constraints in many units. Furthermore, the care provided by a nephrologist to his or her patients may extend over many years, and it is desirable to maintain and build on this therapeutic relationship at difficult time points in a patient's disease trajectory. As a result, it is important that nephrologists develop core palliative care skills such as basic symptom management, including psychosocial assessment, key communication skills, and a general understanding of end-of-life care and managing dialysis withdrawal. This set of skills will allow a nephrologist to manage most aspects of KSC, along with experienced nursing and allied health staff.

Specialist palliative care advice should be sought when basic management is felt to be inadequate at addressing more complex clinical scenarios. Some of these challenging cases can include difficult and refractory symptoms, both physical and psychological, family conflicts, and ethical issues regarding appropriateness of commencing or continuing with dialysis. In these settings, the palliative care team can assist in a consultative service. Knowledge about and regular liaison with local palliative care services is important to allow their involvement when difficult cases arise. Table 51.6 summarizes some aspects of general and specialist palliative care [13].

Shared Decision-making

The Kidney Disease Improving Global Outcomes (KDIGO) consensus conference in supportive care defined shared decision-making as the following:

> "Shared decision making is a process of communication by which physicians and patients agree on a specific course of action based on a common understanding of the patient's treatment goals, taking into account

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Table 51.6 General and specialist palliative care skills.

General palliative care skills for the nephrologist
Basic management of common symptoms in patients with kidney disease
Basic management of depression and anxiety, and psychosocial issues
Discussions about:
• prognosis
• goals of treatment
• ceilings of care
Management of dialysis withdrawal
Basic management of end-of-life care
Specialist palliative care skills
Management of refractory symptoms
Management of more complex depression, anxiety, grief, and existential distress
Assistance with conflict resolution regarding goals of treatment within families, and between families and staff
Assistance in addressing cases of near futility
Management of complex end-of-life care

Source: Adapted from Quill et al. [13].

> the benefits and harms of treatment options, and the likelihood of achieving the outcomes that are most important to individual patients" [3].

Shared decision-making requires the physician to have respect for and curiosity about the patient, to tailor an individualized treatment plan, and to empower patients to be actively involved in their healthcare. In KSC, this is particularly applicable to the decision regarding the initiation of dialysis or to pursue CKM, the withdrawal of dialysis, and advance care planning. Shared decision-making is discussed further in Chapter 71.

Prognosis

Prognosis is an essential part of any shared decision-making process involving a life-limiting illness, as assessing and conveying prognostic information helps patients make informed decisions about their future. Although not all patients wish to know their prognosis, the vast majority of nephrology patients do want life-expectancy information and for the physician to provide this without prompting [33]. Over 90% of patients on dialysis believe it is important to know their prognosis or how their disease will progress [34]. Prognostic information is often the single most important piece of information that patients need to make informed choices [35] and serves as a starting point for patients to consider the risks and benefits of dialysis [8]. Dialysis patients tend to be overly optimistic about their prognosis compared to their nephrologists [9]. Misinformation about prognosis can lead to inappropriately aggressive treatments. Patients with CKD in whom prognosis is particularly poor should be informed that dialysis may not confer a survival advantage, or improve quality of life or functional status over CKM, although cultural and ethnicity factors may influence the willingness to know or participate in such decision-making [3].

Despite observational studies generally showing a survival advantage with dialysis [10, 11, 30, 36], direct comparisons of survival on dialysis and nondialysis pathways are inherently flawed in that dialysis patients are preselected and thus tend to be younger, have fewer extrarenal comorbidities, and have better performance status. In addition, time points from which survival is measured vary significantly between studies, particularly as glomerular filtration rate (GFR) at dialysis initiation is variable. Conservatively managed patients are also a heterogeneous group, consisting of those who are candidates for dialysis but for whom dialysis is not available, those who choose not to have dialysis, and those who are not offered dialysis for various reasons such as comorbidities, advanced age, frailty, lack of capacity or a separate and more advanced life-limiting illness such as cancer, to name a few. Therefore, observations of survival advantage with dialysis over CKM need to be interpreted in such a context.

There is increasing evidence that dialysis does not offer a survival advantage to some patients with ESKD. Observational studies have demonstrated that patients over 75 years of age with a high number of extrarenal comorbidities, particularly diabetes [36] and ischemic heart disease [37], are unlikely to derive any survival advantage with dialysis, compared with those managed on a nondialysis pathway. Similarly, there appears to be no survival advantage for patients aged 80 years old regardless of comorbidities [38, 39], nor for patients with poor functional status (World Health Organization Performance Score 3 or more) [39].

Initiation of Dialysis

It is imperative that nephrologists lead discussions about the appropriateness of dialysis. In addition to prognosis, other aspects that should be incorporated into these discussions include quality of life and anticipated effects of dialysis on physical function, social circumstances, and family and carers. Patients may be willing to trade off significant life expectancy to reduce the lifestyle restrictions imposed by dialysis. In an Australian study, patients were willing to forego 7 months of life expectancy to reduce the number of visits to hospital and 15 months to increase their

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ability to travel [40]. Ethical principles of beneficence and nonmaleficence obligate the nephrologist to weigh potential benefits and harms to the individual patient and plan a course of treatment that is individualized to each patient's unique circumstances. Dialysis should be offered to patients who are expected to benefit, and this includes an expectation of longer survival as well as an acceptable quality of life. Those who would not be appropriate for dialysis or who choose CKM should be offered active alternative care. The epidemiology, content, indications, and decision-making regarding CKM as a treatment option for patients with ESKD are discussed in detail in Chapter 55.

Except in situations of medical emergency, patients commencing dialysis should have informed consent to undergo treatment. The key elements of legally binding consent, in common law jurisdictions, include [41]:

- decision-making capacity
- voluntariness
- provision of adequate information.

Provision of information is vital to allow patients to participate in the decision-making process and make meaningful choices. Adequate information must also include disclosure of any possible alternative treatment, which in the case of dialysis is an explanation of CKM and the material risks associated with dialysis. Material risks include [41]:

- complications of dialysis such as hypotension and sepsis, as well as symptoms such as fatigue
- prognosis (a best estimate by available tools)
- anticipated effect on the life of the patient, family, and carers.

A KSC team can facilitate ongoing discussions and provide support for patients and families. It is essential that patients are aware of an active and viable alternative to dialysis in making their decision to commence dialysis.

Withholding or Withdrawal from Dialysis

Ethical decision-making in the area of RRT has shifted from the early days of "who should be dialysed?" to the more recently pertinent question of "who should *not* be dialysed?" Perhaps the latter question has always been pertinent. Belding Scribner, in his 1964 presidential address to the American Society of Artificial Internal Organs, identified several issues with the introduction of a chronic hemodialysis program. Two of the issues Scribner raised were withdrawal from dialysis – "what criteria to use and to whom to turn to make such a difficult life and death decision" – and dying with dignity and without prolonged suffering [42].

Withdrawal from dialysis is a common cause of death in ESKD patients (Table 51.7). Withholding and withdrawal from dialysis is both legal and ethical if:

- a competent patient has refused to commence or continue dialysis
- the dialysis treatment is of no benefit to the patient.

Withholding and withdrawal of dialysis in these settings do not constitute euthanasia or physician-assisted suicide [43].

If dialysis treatment is of no benefit to the patient, the nephrologist is under no legal or ethical obligation to provide dialysis [43]. The principle of autonomy has been used to justify treatments on the view that doctors ought to provide what the patient requests. However, each of the bioethical principles are important and autonomy does not override the other principles. While patients' wishes and values should be considered, they should not be considered in isolation [44]. Nephrologists should offer treatments that they believe are of benefit to the individual patient but are under no obligation to provide treatment they feel is of no benefit and potentially harmful to the patient. In situations where there is a conflict between the nephrologist and the patient, or the surrogate decision maker, involving the multidisciplinary team and seeking a second opinion regarding diagnosis and prognosis is usually helpful. If the patient is incompetent, the decision should be communicated to the surrogate decision maker, including an assessment of the patient's best interest. Ultimately, disputes can be resolved by appropriate legal channels. The Renal Physician's Association (USA) have formulated a set of recommendations regarding withholding and withdrawing from dialysis, and these serve as a useful starting point to guide physicians. The epidemiology and decision-making regarding dialysis withdrawal as well as the approach to care are discussed in detail in Chapter 55.

Table 51.7 Prevalence of patients who withdraw from dialysis.

United States: Dialysis discontinuation before death [12]		
All ages	23.4%	
Aged 85+	34.2%	
Australia and New Zealand: ANZDATA: % of death listed as due to dialysis withdrawal [16]		
	Australia	New Zealand
Hemodialysis all ages	34.4%	27.6%
Hemodialysis aged 75+	42.1%	52.9%
Peritoneal dialysis all ages	28.8%	27.8%
Peritoneal dialysis 75+	36.2%	39.45

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Ultimately, decisions to forego or withdraw from dialysis can be difficult and fraught with emotions. Sensitive communication with care and empathy from healthcare professions are imperative. It is important to remember the principle of nonabandonment, and to support patients and their families through these times. This is where KSC comes to the fore, emphasizing an active treatment to improve the patients' symptoms while supporting them and their families.

Advance Care Planning

Advance care planning is a process that involves understanding, reflection, communication, and discussion, with the aim of clarifying preferences for end-of-life care for a patient [45]. This often occurs over many conversations between the patient, their family or carer, and their healthcare providers. Advance care planning for patients with advanced CKD has been recommended by clinical practice guidelines in many countries [3, 46, 47]. It provides a broad focus on patient values and goals of care and assists patients in understanding their illness, prognosis, and anticipated disease trajectory. It can include, but is not limited to, an advance care directive, a not-for-resuscitation order, and the appointment of surrogate decision makers. Failure to discuss prognosis and end-of-life preferences can lead to unwanted suffering, continuation of aggressive treatments at the end of life, and patient preferences not being respected. For example, in considering preferences for resuscitation, patients need to be aware that outcomes of aggressive treatments such as in-hospital cardiopulmonary resuscitation (CPR) for dialysis patients are poor, with less than one-third surviving in one study and most survivors being discharged to care facilities [48].

In patients planned for CKM, advance care plans can set out their wishes not to be dialysed as well as their preferences for other forms of life support. For patients on dialysis, discussions around resuscitation and withdrawal from dialysis remain important aspects, and structured programs in dialysis units have proven success in increasing the number of patients with plans in place [49]. In addition, discussions need to focus on how illness and interventions affect the individual, his or her life, relationships, and what he or she values most [45]. Open and honest discussions about the future can empower patients, enhance hope, and alleviate fears [50].

Studies show that patients would like their nephrologist to initiate advance care planning conversations [45, 51]. However, barriers to these discussions include system factors such as fragmented medical care across many providers as these patients have complex diseases processes, a lack of communication among the providers, and an unclear locus of responsibility [52]. Clinician factors also hinder effective advance care planning (ACP) such as nephrologists' lack of training in communication, a lack of available time, and the mistaken perception that ACP may cause harm by destroying hope [14, 47]. For further discussion of ACP in CKD please refer to Chapter 54.

Conservative Kidney Management

CKM is an active care pathway for patients with ESKD for whom dialysis was unlikely to be beneficial and who chose not to pursue dialysis. It comprises holistic, patient-centered care that actively manages patients' physical, psychosocial, and spiritual needs. The principle of nonabandonment is fundamental, which means that nephrologists continue to play an important and ongoing part in the patients' care with the added support of palliative care physicians and allied health staff. The key components of CKM are outlined in Table 51.8 and are fully discussed in Chapter 55.

It is difficult to estimate the incidence or prevalence of patients on a conservative nondialysis pathway. An Australian population-based study from 2003 to 2007, linking mortality data for the general population to ANZDATA of patients receiving RRT, suggested that for every new patient in Australia who died receiving RRT (dialysis or transplant), there was one new patient who did not [53]. The majority of those who did not receive RRT were older, with more than 80% over the age of 70 years. Similarly, a Canadian cohort study showed that in adults aged over 75 years, untreated kidney failure was 2–10-fold more common than in those treated with dialysis [54]. There is increasing data around survival for those on a nondialysis pathway. A large Australian prospective study reported that conservatively managed patients ($n = 122$) with an average age of 82 years survived a median of 16 months and about one-third survived 12 months past a time when

Table 51.8 Components of conservative kidney management.

Patient-centered holistic care for patients with ESKD
1) Interventions to delay progression of CKD and minimize risk of adverse events or complications, including nutritional assessment and management
2) Shared decision-making and communication, including advance care planning
3) Active symptom management
4) Psychosocial and family support
5) Cultural and spiritual domains of care
Does not include dialysis

Source: Adapted from Davison et al. [3].

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dialysis might otherwise have been indicated (eGFR < 10 ml/min) [30]. For a full discussion on CKM refer to Chapter 55.

Communication

Clinician-led conversations about patient preferences, goals, values, and expectations form an important part of patient-centered care. It is essential that clinicians working within the KSC framework are proficient in engaging in conversations about a range of serious and important topics, including choice to pursue a dialysis or CKM, prognosis, goals of care, CPR, withdrawal from dialysis, adverse health outcomes from nonrenal comorbidities, advance care planning, and transitioning to end-of-life care. Eliciting a patient's big picture goals in these conversations can be accomplished by exploring hopes and expectations, identifying concerns about the future, and determining situations in which the patient would consider forgoing a life-supporting therapy such as dialysis [8]. Having good communication around these issues can enhance goal-consistent care such as dying in a preferred setting, reduced hospitalization, and less aggressive care at the end of life. This may also improve outcomes for families without an increase in patient distress or anxiety [55]. Some specific time points and triggers for these conversations are listed in Table 51.9 [8, 55, 56].

Communication is a two-way process and provision of information, likewise, is not a unidirectional flow of facts from the physician to the patient. The *Ask-Tell-Ask* approach (Table 51.10) can be a useful framework for providing information. It focuses on two-way interactions and ensuring adequate understanding of provided information [57]. These conversations can be emotional and potentially confrontational. It is useful to have a structured approach so that conversations address the critical issues. One way of structuring a serious illness conversation is outlined in Table 51.11 [58].

Goals of care should be reassessed regularly, especially as clinical situations change. It is important to have these conversations in a private setting without time constraints. Busy nephrology clinics or dialysis units surrounded by other patients and staff are not ideal settings. Documentation of the conversation is critical to ensure the content is recorded correctly and will be accessible at a later date. This may include documentation within electronic medical records, dialysis units' records, personal copies given to patients, and forwarded communication to family physicians and other specialists involved in the patient's care.

Table 51.9 Triggers for initiating discussions about dialysis or conservative kidney management.

Triggers [8, 55, 56]
• At time of referral for dialysis (discussion is necessary to ensure informed consent for dialysis)
• Patients considering CKM
• "No" to the Surprise Question (would you be surprised if this patient died in the next 12 months?)
• Worsening or high symptom burden
• Worsening or poor QOL
• Multiple or prolonged hospital admissions
• Functional decline, increased dependence or moving into long-term care facility
• Unintentional weight loss/progressive malnutrition
• Repeated dialysis access complications
• Unable to tolerate dialysis
• Cardiovascular events: myocardial infarction, cerebrovascular events, amputations
• High comorbidity: extensive cardiovascular disease, malignancy, cirrhosis, chronic lung disease
• Patient or surrogate decision-maker request to stop dialysis

CKM, conservative kidney management; QOL, quality of life.

Table 51.10 Ask-Tell-Ask framework.

Ask-Tell-Ask	
Ask	Asking what the patient understands before giving information is useful as patients have different levels of understanding and may desire different levels or amounts of information. In particular, it is useful to ask the patient if and how much prognostic information they desire before providing it.
Tell	In providing serious or confronting information such as poor prognosis, it is helpful to start with a "warning shot" such as "I am worried about how sick you are". This helps patients better prepare cognitively and emotionally for potentially distressing news. Sometimes this is best stated at one consultation before the more detailed information is provided at the next. Information should be given in direct and plain language, appropriate for the patient's educational level and avoiding medical terminology. No more than three pieces of information should be given at any one consultation.
Ask	Asking the patient about the information given can reinforce the information as well as assess understanding and correct misconceptions. It is also an opportunity to invite patients to ask questions.

Source: Adapted from Schell and Arnold [57].

Conclusion

KSC is an active approach to kidney care that integrates palliative care principles with nephrology to provide holistic, patient-centered care to a worldwide growing population of patients with CKD, typically those who are

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Table 51.11 Suggested content for serious illness conversations.

Structure for serious illness conversations with some examples	
Understanding of illness	"What do you understand about your health and what lies ahead?" "What do you think starting dialysis means for your future health and quality of life?" "How has your recent hospitalization changed your understanding about your health in the future?"
Information preferences	**How much information and in what form** "Do you want me to talk about what lies ahead for you and your health?"
Prognosis	**Depending on information preference** "Sometimes patients wonder about how long they might have. Is that something you would like me to share with you?" **Acknowledge uncertainty** "I can't predict exactly what would happen, and based on available information, I would say weeks to a short number of months/a few months to a year/1 or 2 years/a few years." "I wish I could tell you things will get better, but we need to prepare for. . . if your health declines suddenly OR if your time is short OR if how you feel now is as good as you will be."
Goals	"What are your most important goals for your life and your health?" "What do you hope dialysis will accomplish for you?"
Fears/worries	"What worries you the most?" "What worries you the most about. . . starting dialysis OR stopping dialysis OR the future OR your illness?"
Function	**What abilities are critical for reasonable quality of life** "What functions or activities are so important that you can't imagine living without them?"
Trade-offs	**How much are you willing to go through for the possibility of more time** "What are you willing to go through to achieve your goals?" "Is dialysis something you are willing to go through to achieve. . .?"
Family	**How much families know about patient's wishes and preferences** "Have you shared your thoughts/health problems/fears/preferences with your loved ones?" "Would you like your medical team to discuss this with your family?"

Source: Adapted from Bernacki et al. [58].

older, comorbid patients with advanced CKD, a high symptom burden, and poor quality of life. It leads a paradigm shift within nephrology that redirects the focus to shared decision-making, quality of life, and providing an individualized care pathway for vulnerable patients. It is an evolving field arising out of increasingly robust evidence-based practice. Ongoing research will be essential to further explore areas of uncertainty and develop more nuanced approaches to care as well as to improve outcomes.

Nephrologists should receive KSC training and incorporate it into their core skill set, much like hypertension management or dialysis prescription. This will ensure that nephrologists always see CKM as the third potential pathway for management of patients with ESKD, alongside transplantation and dialysis. It is now imperative for kidney units to incorporate KSC into their standard of care with the aim of providing appropriate, individualized, and active management of all CKD patients at all times in their lives.

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52

Symptoms

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Introduction

Kidney supportive care is care aimed at improving the quality of life (QOL) for patients with chronic kidney disease (CKD) throughout the continuum of their illness. A key component of this is meticulous physical and emotional symptom assessment and management [1]. The high symptom burden experienced by patients with CKD throughout their illness trajectory can be extremely debilitating and negatively impacts their QOL and functional capacity. Recent patient engagement has highlighted symptom management as a top research priority for people with advanced CKD [2]. Symptom assessment and management need to be integrated into routine kidney care early and readdressed throughout the patient's illness.

This chapter summarizes the evidence surrounding the epidemiology and impact of symptoms in patients with CKD, and outlines general approaches and tools to assess and manage the symptom burden.

Epidemiology

Prevalence of Symptoms in Advanced CKD and ESKD

People with CKD tend to experience many symptoms such as fatigue, pain, pruritus, restless legs, anorexia, nausea, insomnia, anxiety, and depression [3–8]. While there is tremendous variability in patients' symptom burden, taken as a whole the number and severity of symptoms have been described as being similar to those of cancer patients hospitalized in palliative care settings [9]. The symptom burden is high across age, gender, race, and geographic location. Syndromes such as malnutrition, protein energy wasting, and frailty are also common, leading to muscle and fat loss and cachexia [10]. These factors exacerbate symptom burden and together they profoundly compromise patients' functional capacity and QOL. While dialysis may address some symptoms such as fatigue, anorexia, nausea, and vomiting, especially for more robust individuals with limited comorbidity, it appears to do little to address symptoms in older more frail patients or those with multimorbidity. For some patients, dialysis may add to overall symptom burden. In the meantime, chronic inflammation, malnutrition, and frailty continue to progress regardless of whether dialysis is started or not.

A comprehensive review of the literature identified that the average number of symptoms per patient ranges between six and 20 depending upon the screening tool used [11]. These data came predominantly from hemodialysis patients, with only very small numbers of patients with stages 4 and 5 CKD not on dialysis. There was a high prevalence for almost all symptoms. The five most prevalent symptoms regardless of CKD stage were fatigue or lack of energy 81% (49–100%), feeling drowsy 75% (49–82%), pain 65% (38–90%), pruritus 61% (33–84%), and decreased appetite 57% (9–83%) [11].

More recent studies have begun to explore further the symptom burden in patients with stages 4 and 5 CKD who have yet to start dialysis. Using a cross-sectional design, 436 people with CKD were recruited: 75.5% were receiving dialysis (hemodialysis = 287, peritoneal dialysis = 42) and 24.5% were not undergoing dialysis (stage 4 = 69, stage 5 = 38) [12]. Of the 32 possible symptoms assessed, participants reported an average of 13.01 ± 7.67 symptoms. Consistent with the prior comprehensive review the most prevalent symptoms across all CKD groups were fatigue

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(77.0%), bone or joint pain (60.3%), pruritus (59.6%), and decreased appetite (50.5%). However, the five symptoms found to be most distressing across all CKD groups were fatigue, bone or joint pain, feeling irritable, restless legs, and decreased interest in sex. Fatigue and bone or joint pain were the most prevalent and distressing symptoms in CKD stages 4 and 5 CKD regardless of whether they are receiving dialysis or not. Figure 52.1 outlines the overlap in the most common and distressing symptoms reported by patients with CKD.

Overall Symptom Burden Does Not Necessarily Improve after Dialysis Initiation

It is generally assumed that patients with end-stage kidney disease (ESKD) who start dialysis will experience a substantial improvement in physical and psychological well-being. However, when studied at a population level, overall symptom burden does not improve for patients on dialysis. The mean number of symptoms reported by patients on dialysis was more than double the number of symptoms reported by patients with stages 4 and 5 yet to start dialysis (14.7 ± 7.5 vs. 7.5 ± 5.3, $P < 0.001$). [12] Perhaps more importantly, overall symptom distress was higher in the dialysis group ($P < 0.001$). Mean overall symptom severity was highest in patients on hemodialysis followed by patients on peritoneal dialysis, then stage 5 (22.09) with the lowest severity scores in stage 4 ($P < 0.001$) [12]. There may be some slight differences in the distribution of symptoms experienced by CKD stage. While earlier reports, based on very limited data, suggested that people with stages 4 or 5 CKD not on dialysis may experience more psychological problems such as worrying, nervousness, irritability or sadness than those who are receiving dialysis [11], more recent work does not support this. The increased symptom burden in dialysis patients appears to be driven primarily by physical symptoms, as there were no significant differences in the distress levels of psychological symptoms such as feeling sad, worried, anxious, nervous, or depressed among CKD stages [12].

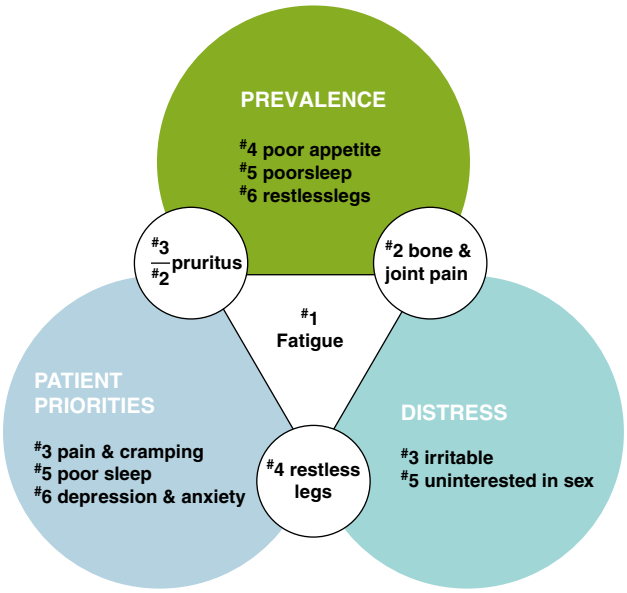

Figure 52.1 The most prevalent, distressing, and highly prioritized symptoms reported by patients with advanced CKD.

Symptom Prevalence in Patients Who Have Chosen CKM

Symptom burden is high but similar for patients who have chosen conservative kidney management (CKM) compared to those on dialysis. The most common symptom reported continues to be fatigue ($n = 191$, 77%) followed by itch (67%), pain (62%), shortness of breath (61%), and edema (54%) [13–17]. The prevalence of other symptoms continues to be high, such as loss of appetite (51%), problems sleeping (51%), and restless legs (33%). Although the prevalence of symptoms may be high, they are not necessarily severe and can be treated. For example, although pain was experienced by 69% of CKM patients, only 26.1% reported their pain as moderate or severe [13, 16, 17]. A qualitative study of patients managed conservatively emphasized the burden of edema, pain, fatigue, and shortness of breath for these patients [18]. Symptom burden appears to be relatively stable until the last month before death but as the disease progresses difficulty concentrating, shortness of breath, and swelling of the legs and arms become more prevalent and may be indicators of near death [11, 16].

Symptom Prevalence in Earlier Stages of CKD

More recently, a few studies have examined symptom burden in earlier stages of CKD. Twenty-five symptoms were assessed in a cohort of 1118 patients with stages 1–5 CKD [15]. CKD stages were categorized as "Early stage" and included CKD stages 1, 2, and 3, "Stage 4", "Stage 5 – Non Dialysis", and "Stage 5 – Dialysis". Overall the prevalence of symptoms was similar and high, irrespective of the stage of the CKD. The most prevalent symptoms in early stages of CKD were bone and joint pain (86%), feeling irritable (77%), and muscle cramps (71%) [15]. In keeping with prior studies, the most prevalent symptoms among those in stage 5 and on dialysis were restless legs, bone and joint pain, and feeling irritable [15]. While bone and joint pain was the most prevalent symptom for the entire cohort (88%), decreased sexual interest was the most severe. Joint

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pain and impaired sexual desire/ability were also the most prevalent symptoms among 35 CKD patients who were in stages 2 and 3 of the disease [19]. Similarly, symptoms were common in a cohort of 283 CKD stage 1–5 patients with a mean eGFR of 38 ml/min/1.73 m^2. The median number of symptoms reported was six out of 11 assessed symptoms (interquartile range 3–8) [20]. Consistent with dialysis patients, the most prevalent symptoms were excessive tiredness (81%) followed by sleep disturbance (70%) and pain in the bones or joints (69%). Clearly, patients in all stages of CKD experience high symptom burden.

Symptom Prioritization

Given the high prevalence of bothersome symptoms, surprisingly little work has been done to understand how patients prioritize symptoms. The international Standardized Outcomes in Nephrology – Hemodialysis (SONG-HD) initiative generated a consensus-based prioritized list of core outcomes for trials in hemodialysis. Symptoms were ranked extremely highly by patients. Fatigue was one of the highest prioritized outcomes and has subsequently been identified as one of five core outcome domains [21]. Pain, sleep, depression, and anxiety were also ranked highly. A Canadian study of key stakeholders, including patients and caregivers, sought to determine research priorities for patients on or nearing dialysis. Symptoms ranked highly and were the focus of three of the top 10 priorities [2]. These involved determining the causes and effective treatment(s) of, and ways to prevent, itching in dialysis patients, the best ways to manage symptoms in people receiving or nearing dialysis, including poor energy, nausea, cramping, and restless legs, and the causes and effective treatment(s) of depression in dialysis patients.

Finally, a small sequential exploratory mixed methods study undertook to identify hemodialysis patient-prioritized symptoms. They found that the top prioritized physical symptoms were insomnia, fatigue, and muscle cramping and the top prioritized mood symptoms were anxiety, depression, and frustration [22]. Participants indicated that symptom frequency, duration, unpredictability, and social and financial effects factored the most into symptom prioritization. To summarize, the most prevalent, distressing, and highly prioritized symptom reported by patients with CKD id fatigue (Figure 52.1). This is followed by pain across all three domains, and then pruritus. Several other symptoms are highly ranked, but vary in importance depending on the domain assessed.

Predictors of Symptom Burden

Overall, few significant associations have been found between biochemical markers of disease severity and symptom burden [8, 11, 23]. Although several studies have not identified an association with gender, the larger more recent studies have showed that being female was independently associated with greater symptom burden [11, 12].

Although there is no consistent relationship between symptoms and CKD stage there does appear to be a moderate trend in the number of symptoms by worsening CKD stage [15, 20] and that being dialyzed or being a CKD stage 5 patient are independently associated with greater symptom burden when compared to predialysis stage 5 CKD patients and patients with less advanced CKD, respectively [12].

Symptom Clusters

Patients with CKD and ESKD often experience symptoms in clusters. Symptom clusters refer to concurrent symptoms related to each other. Theoretically, symptoms within a cluster could have a synergistic relationship. Identification of related clusters of symptoms could provide insight into underlying determinants of the symptom experience that help guide clinical management.

Research into symptom clusters for patients with CKD is extremely limited. Three clusters were identified using principal component analysis based on the 12 symptoms within the symptom problem list of the KDQOL-SF in a study of 1553 incident hemodialysis and peritoneal dialysis patients [24]. These clusters are described in Table 52.1. All clusters showed strong negative associations with QOL dimensions and functional status. Only serum albumin and hemoglobin were significantly correlated with all three clusters, which may hint at underlying pathophysiology such as systemic inflammation (discussed further below). The patient-reported "uremic symptoms" were not related to objective clinical indicators of uremia as we currently understand them and there were no significant associations with other clinical variables.

Table 52.1 Symptom clusters in CKD.

Cluster[a]	Symptoms
General symptoms of uremia	Shortness of breath Feeling faint/dizzy Poor appetite Feeling "squeezed out" Feeling nauseous
Neuromuscular problems	Sore muscles Chest pain Numbness in the hands/feet
Skin problems	Itch Dry skin

[a] Cluster names are not accurate reflections of the underlying pathophysiology.

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Pathophysiology

The underlying pathophysiology of symptoms in CKD is poorly understood. Little has been done to determine the role of potential uremic toxins and other biomarkers. Biochemical abnormalities do not appear to be the major drivers. There are likely multiple coexisting mechanisms involved. For example, while anemia may exacerbate fatigue, exertional dyspnea, weakness, and weight loss, there is no specific hemoglobin level at which patients start to experience symptoms. In the current era of high flux dialyzers and phosphate binders, serum phosphorous is not predictive of the presence or severity of pruritus [25]. However, high serum calcium and phosphorous may lead to periarticular calcification, pseudo-gout or gout, and ruptured tendons, all of which can result in pain. Although iron deficiency, anemia, and high serum phosphorus levels may contribute to restless legs syndrome, these associations are inconsistent and it is unclear for whom biochemical abnormalities exacerbate symptoms [26–28].

Systemic inflammation is felt to contribute to many of the symptoms experienced by patients with CKD. It is also likely a major driver behind protein energy wasting, malnutrition, and overall functional decline [29]. Inflammation also contributes to low serum albumin and anemia, the biochemical abnormalities that appear associated with symptoms. Skin and peripheral nerve abnormalities have been implicated for both uremic pruritus [30, 31] and restless legs syndrome [32]. These are also suspected to be due to or exacerbated by chronic inflammation. Other abnormalities, such as an increase in activity of μ-opioid receptors, have been implicated as a possible mechanism for uremic pruritus [33, 34]. The mechanisms underlying these symptoms are likely complex, multifactorial, and inter-related. The relative contribution that each has in symptom experience likely varies enormously between patients. This may explain the tremendous interpatient variability in symptom burden and overall functional trajectory.

Psychological factors are likely extremely important determinants of symptom prevalence and severity given that symptoms are defined as the subjective perceptions of physical, emotional, or cognitive changes as experienced by the patient. Therefore, perceptions of symptom burden may be influenced to a greater degree by psychological factors such as personality or cognitions than physiologic abnormalities [24]. Further details on pathophysiology are described for individual symptoms in Chapters 72–77.

Given our poor understanding of the etiology of symptoms, we have limited means to prevent them. We lack biomarkers to predict onset and progression and we lack effective treatments that target the underlying causes. The necessary psychological supports are not fully understood, tend to be resource intensive, and are typically absent in the routine care of patients with CKD.

The Negative Impacts of Symptoms

Symptom burden is correlated highly with impaired physical and mental QOL in patients with CKD and appears much more important than objective clinical and dialysis characteristics [8, 24, 35–37]. Symptom burden was shown to account for 29–39% of the impairment in dialysis patients' physical QOL scores and 39–43% of their impairment in mental QOL scores in 1098 dialysis patients [3, 35]. Moreover, changes in symptom burden were shown to account for 34–45% of the change in physical QOL and 46–49% of the change in mental QOL in 852 dialysis patients [8, 35]. Similarly, the three previously described symptom clusters accounted for 49% of the variance in QOL scores [24]. The effect of a cluster of symptoms on QOL may be more significant than the effect of an individual symptom [24], a concept widely reported in other chronic health conditions [38]. In addition, symptom burden correlates with depression [11, 37]. Symptoms and QOL of dialysis patients have also been associated with, albeit inconsistently, worsened hospitalization and mortality rates [39]. Given that QOL remains poor, especially for patients on dialysis, and that patients give high priority to symptom management and QOL, symptom reduction is of critical importance in the care of patients with CKD.

Healthcare Provider Education and Attitudes toward Symptom Management in CKD

There are gaps in the skill sets taught in nephrology training that will need to be addressed if we are to provide high-quality kidney care. Most nephrologists have limited expertise in symptom management and feel unprepared to pursue effective treatment options. Some feel that it is not their responsibility to treat symptoms that are not directly related to the CKD or dialysis [40]. Two recent surveys of renal fellows reported that they received little education in the principles of kidney supportive care; only 44% of fellows reported being taught explicitly how to treat dialysis patients' pain [41] (although this had increased from 30% in 2003 [42]) and only 9.4% felt very comfortable treating pain in patients with advanced CKD [43]. However, nearly all thought it was important to provide this care. Clearly, enhanced education in symptom management will be

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required to address the symptom burden and suffering experienced by patients with CKD. As a community, we will also have to take responsibility for overseeing symptom management, whether we take primary responsibility or coordinate and share care with other multidisciplinary care providers.

Symptom Screening

Symptom recognition by health professionals caring for patients with CKD is inadequate [40]. When healthcare providers rely on standard consultations, they demonstrate poor sensitivity to patients' symptoms and only weak agreement with their ratings of severity [44, 45]. To address this, Kidney Disease: Improving Global Outcomes (KDIGO) recommends incorporating regular global symptom screening using validated tools into routine clinical practice [1]. Given the high prevalence of symptoms among patients with stages 3–5 CKD and ESKD, whether they are treated with dialysis or CKM, screening for symptoms is appropriate throughout the illness trajectory, starting in the earlier stages of the disease.

There are several aspects of symptom screening and assessment worth consideration. Symptoms are subjective; they are what the patient states them to be. Conceptually, symptoms are a multidimensional construct characterized by prevalence, distress, severity, and frequency. The symptom experience is better understood when considering the multidimensional nature of physical and psychological symptoms. The symptom burden therefore reflects the magnitude of the individual's perceptions of frequency, intensity, and distress of the symptom, totaled for all reported symptoms.

Symptom burden, however, is not necessarily synonymous with symptom suffering. The more encompassing symptom experience and the related suffering is unique for each individual and is modulated by contextual, cognitive, and emotional factors [46]. People develop cognitive models to explain their symptoms, how and why they occur, and what measures can prevent or control them. These cognitive models reflect their knowledge and personal experiences and influence directly the individual's response to physical and psychological symptoms. Exploring patients' (mis)perceptions of symptoms can assist patients in selecting appropriate self-management strategies. Emotional responses, especially fear and uncertainty, also impact suffering. Some patients may be predisposed to respond fearfully to a troublesome situation rather than to the experience of the symptom itself. This is particularly relevant for pain. Emotional distress when combined with negative cognitive evaluations like anticipation of upcoming severe pain or reflections on how harmful or difficult it may be to endure the pain over time may induce considerable suffering even with low pain severity.

Culture factors into the symptom experience. All cultures generate explanatory models that attempt to account for the phenomenon of illness and influence patients' beliefs around illness and suffering [47]. Culture also plays a role in the expression of suffering, with many cultures being reluctant to complain of symptoms such as pain or depression as they may be seen as signs of weakness [47]. South Asian patients often described experiencing symptoms with a greater severity than other cultures [20]. Some cultures are not comfortable with frank, direct styles of communication and therefore may not express suffering overtly as this may be seen as inappropriate. In these cases, emotional containment does not mean a lack of suffering.

Routine screening for symptoms helps to refocus care to a more patient-centered model. These assessments not only identify the presence of symptoms but also provide the opportunity for difficult discussions about appropriate supportive care options. Listening to the patient validates the significance of their symptoms and their suffering, and is an important part of the therapeutic intervention. Patients with CKD have voiced a desire for greater dialogue with their providers around symptoms, noting that such acknowledgement and engagement might improve the symptom experience [22]. The potential benefits to integrating routine symptom management are outlined further in Table 52.2.

Table 52.2 Potential benefits of integrating routine symptom screening.

Identifies and reduces symptoms, minimizes disability, and improves QOL
Encourages patient and caregiver engagement
Acknowledging symptoms and their impact on the patient's life is an important part of the therapeutic intervention and may have health benefits in itself
Increased patient satisfaction by acknowledging and validating their suffering
A "communication" tool that assists clinicians in providing individualized, patient-centered care by aligning care with what matters most to a patient
Provides data to evaluate clinical practices and policies
Allows for assessing and comparing the quality of care providers and clinics
Considers and evaluates patient-reported outcomes such as symptoms increases public accountability of health services and healthcare professionals

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Symptom Screening and Assessment Tools

Many global symptom screening and assessment tools of varying length and utility have been used in CKD. Most experience with tools comes from research studies rather than clinical implementation. For clinical utility it is important that tools be short and simple to minimize patient and staff burden. They must also be appropriate for use in high-risk patients such as those who are frail and those with cognitive impairment. Lastly, the tool should be relevant to patients with CKD, reliable, valid, and sensitive to change.

Broadly, symptom assessments can be characterized as either one-dimensional vs. multidimensional or disease specific vs. generic. One-dimensional tools such as rating symptom severity are useful for symptom screening given their simplicity. This allows for routine and regular use. A good example would be the Edmonton Symptom Assessment System – revised: Renal (ESAS-r:R) as seen in Figure 52.2. However, once a symptom is recognized, several core domains should be assessed: intensity, impact on function, and impact on QOL. This may mean better understanding the frequency and level of distress or intrusiveness of the symptom. This requires careful communication with the patient that can be facilitated by a multidimensional symptom assessment tool. Disease-specific tools are tailored to the symptoms and concerns of a specific condition. Generic tools consider general symptoms or concerns that are common to many conditions. Often both types are used, the former having greater face validity and credibility, the latter allowing comparisons across conditions.

Several global symptom screening and assessment tools have been used for patients with CKD. These instruments vary in the types of symptoms assessed: either mental or physical symptoms or both, the number of symptoms included, and the time period over which the symptoms were experienced. These differences make a comparison between studies difficult.

Evidence for validity or reliability is limited for several of them. Table 52.3 outlines recommendations for tools that can be used in routine clinical care and for clinical studies with patients with CKD.

The instruments typically used to screen for symptoms are one-dimensional, focusing on the presence and severity of symptoms. Most are disease-specific. They were originally developed for palliative cancer patients and were subsequently adapted for use with patients with CKD, ensuring the inclusion of relevant symptoms such as problems sleeping, pruritus, and restless legs. Several formats have been used: visual analogue scales (VAS), numerical rating scales (NRS), and Likert scales, often referred to as verbal rating scales (VRS). A VAS consists of a horizontal line, usually 10 cm (or 100 mm) in length, that is anchored with verbal descriptors. A NRS is a segmented version of the VAS in which a respondent selects a whole number that best reflects the intensity of the relevant symptom. Likert scales ask respondents to select the verbal descriptor that best reflects their symptom severity. Patients may interpret different formats differently, which limits the ability to compare findings across populations. Examples of the different severity formats are outlined in Figure 52.3. For some symptoms, such as pain, a 0–100 mm VAS or a 0–10 NRS is advised based on extensive literature around what constitutes clinically important differences in pain intensity. Consensus from the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) was to recommend using a 0–10 NRS in pain studies [58].

Assessment tools specific to individual symptoms have been developed and are discussed in Chapters 72–77. Several self-report QOL measures have been used for patients with CKD and these include multidimensional assessments for physical and emotional symptoms. They also address issues such as burden of disease and effects on daily life, quality of social interactions and social support, and patient satisfaction. Unfortunately, they are more burdensome and are difficult to integrate into routine clinical care in a manner that is responsive to an individual patient at any given clinical encounter. To fully integrate symptom assessments into routine care, simple tools that can be interpreted and completed easily by patients, caregivers, and staff are required [59, 60].

General Approach to the Management of Symptoms

Evidence-based interventions for specific symptoms are discussed in detail in Chapters 72–77. It is important, however, to understand a general approach to symptom management. Key elements to this approach are outlined in Table 52.4. The aim of treatment is to ameliorate symptoms that are burdensome and adversely impact the patient's QOL, as it is not always necessary or possible to resolve them completely. It is important to acknowledge this and negotiate with the patient an acceptable level of symptom control. While there may be variability between patients, there is good evidence in pain research to suggest that targeting a final pain state of less than 33/100 mm on a VAS or 3/10 on a NRS or a change in pain intensity of at least 30% (moderate benefit) or 50% (substantial benefit) will deliver worthwhile QOL benefits [61, 62]. Evidence for

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Edmonton Symptom Assessment System Revised: Renal (ESAS-r:Renal)

Please circle the number that best describes how you feel NOW:

No Pain	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	Worst Possible Pain
No Tiredness *(Tiredness = lack of energy)*	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	Worst Possible Tiredness
No Drowsiness *(Drowsiness = feeling sleepy)*	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	Worst Possible Drowsiness
No Nausea	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	Worst Possible Nausea
No Lack of Appetite	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	Worst Possible Lack of Appetite
No Shortness of Breath	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	Worst Possible Shortness of Breath
No Depression *(Depression = feeling sad)*	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	Worst Possible Depression
No Anxiety *(Anxiety = feeling nervous)*	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	Worst Possible Anxiety
Best Wellbeing *(Wellbeing = how you feel overall)*	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	Worst Possible Wellbeing
No Itching	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	Worst Possible Itching
No Problem Sleeping	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	Worst Possible Problem Sleeping
No Restless Legs	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	Worst Possible Restless Legs
No _____ Other Problem *(for example constipation)*	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	Worst Possible _____

Patient's Name _____

Date _____ Time _____

Completed by (check one):
- ☐ Patient
- ☐ Family caregiver
- ☐ Health care professional caregiver
- ☐ Caregiver-assisted

Body Diagram on Reverse

Developed by the Edmonton Zone Palliative Care Program and Northern Alberta Renal Program
Revised 2016-11

Figure 52.2 The Edmonton Symptom Assessment System – revised: Renal.

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Please mark on these pictures where it is that you hurt:

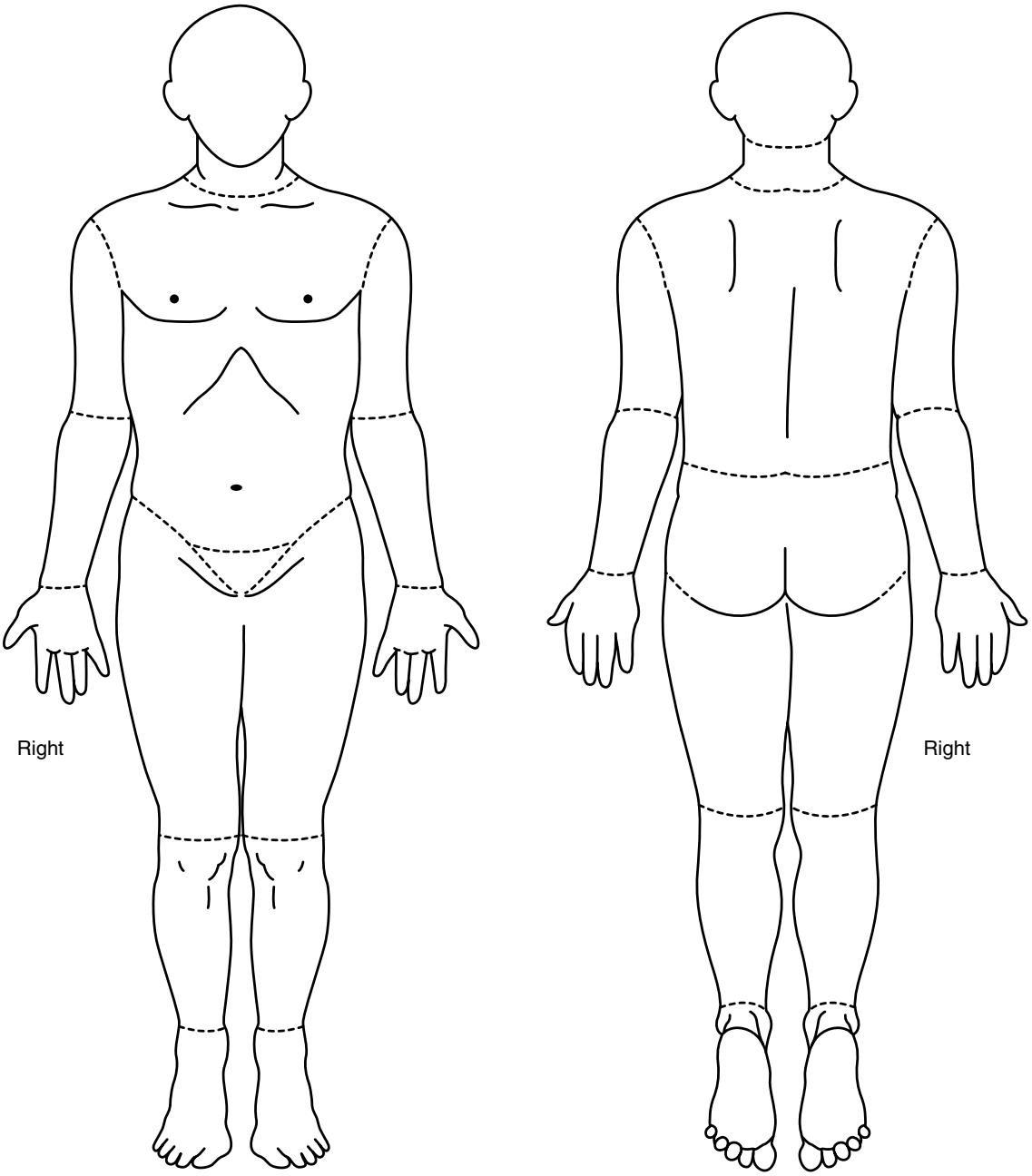

Figure 52.2 (Continued)

other symptoms is not as robust but may follow a similar pattern.

Given the synergistic and interrelated nature of symptoms experienced in advanced CKD, an approach to care that addresses overall symptom burden is likely to improve QOL even if each individual symptom has not resolved completely. A single symptom may be the root cause for several symptoms and identifying this root cause can help focus therapy. For example, a moderate reduction in pain may be sufficient to improve sleep, improve mood, and increase active coping strategies, resulting in a meaningful improvement in function and QOL. When restless legs or pruritus is recognized and well-managed, other symptoms may improve, such as quality of sleep, depression, and fatigue.

A general stepwise approach to symptom management is strongly advised and involves (i) ruling out contributing

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Table 52.3 Global symptom screening and assessment tools for use in patients with CKD.

Symptom assessment tool	Description	Recommended uses
Edmonton Symptom Assessment System – revised: Renal (ESAS-r:R) [3, 8, 48]	• A self-report tool that assesses the prevalence and severity of 13 symptoms using VAS with a superimposed 0–10 NRS for pain, activity, nausea, depression, anxiety, drowsiness, appetite, wellbeing, shortness of breath, pruritus, sleep, and restless legs. The tool provides an opportunity for other symptoms to be added by patients. • The scale for each symptom is anchored by the words "no" and "severe" at 0 and 10, respectively. • The sum of all scores make up the overall symptom distress score ranging from 0 to 130, with higher scores indicating greater symptom severity. • A caregiver can complete several of the items if the patient is too ill to participate in the evaluation. • This instrument is depicted in Figure 52.2	This tool is freely accessible [48]. It has strong evidence for validity. It is short, practical, and can be rapidly and repeatedly completed by patients and therefore incorporated easily into routine clinical care, even for patients who are preterminal. The ESAS-r:R has been translated into several languages. A further advantage is that caregivers can provide validated information in situations where patients become too ill to report their problems.
Palliative Care Outcome Scale – Renal (POS-renal) [49, 50]	• A self-report tool that assesses 17 symptoms: pain, shortness of breath, weakness or lack of energy, nausea, vomiting, poor appetite, constipation, mouth problems, drowsiness, poor mobility, itching, difficulty sleeping, restless legs or difficulty keeping legs still, anxiety, depression, changes in skin, and diarrhea. • Symptoms are rated in terms of their impact on the patient over the last week from 0 (not at all) to 4 (overwhelmingly). • There are also additional questions covering carer anxiety, practical issues, and optional items for any other concerns. These include items such as "family/friends anxious about you," "able to share with family/friends," "as much information as you wanted," "practical problems addressed," and "time wasted on appointments." • There is a patient and staff version. The patient version was recently validated against the ESAS-r:R and the KDQOL-SF v. 1.3 [51].	This symptom screening tool is longer than the ESAS-r:R but is still simple to use and can be incorporated relatively easily into routine clinical care, even for patients who are preterminal. It has been translated into several languages. A further advantage is that the staff version may be helpful in situations where patients become too ill to report their problems.
Dialysis symptom index (DSI) [52]	• A self-report tool that assesses the prevalence and severity of 30 symptoms: constipation, nausea, vomiting, diarrhea, decreased appetite, muscle cramps, leg swelling, shortness of breath, light-headedness, restless legs, numbness, feeling tired, cough, dry mouth, bone or joint pain, chest pain, headache, muscle soreness, difficulty concentrating, dry skin, itching, worrying, nervousness, trouble falling asleep or staying asleep, feeling irritable, sad or anxious, decreased interest in sex, and difficulty becoming sexually aroused. • Symptoms are rated from 1 (not at all bothered) to 5 (very much bothered). • Total score ranges from 0 to 150, with higher scores indicating greater symptom severity.	The tool is easy to use. Respondent burden is slightly greater than for ESAS-r:R but similar to POS-renal and less than the multidimensional HRQOL tools that incorporate symptom assessments. There is limited experience with it being incorporated into routine clinical care for symptom screening.
Physical symptom distress scale (PSDS) [53]	• A self-report tool that assesses the prevalence and severity of 16 symptoms: numbness or tingling, impaired visual ability, swelling in feet, stiffness of joints, constipation or diarrhea, dizziness, headache, pain, and muscle cramps. • Patients rate severity on a four-point Likert scale: 0 = not bothered at all, 4 = extremely bothered.	There is limited experience with this screening tool or evidence for validity. There is some redundancy with respect to items pertaining to pain. However, it appears practical and simple enough to incorporate into routine clinical care.

(*Continued*)

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Table 52.3 (Continued)

Symptom assessment tool	Description	Recommended uses
The CKD Symptom Burden Index (CKD-SBI) [54] see Supplemental Material 1	• This tool is a modification of the DSI. It is a self-report instrument that assesses the prevalence, distress, severity, and frequency of 32 symptoms and provides an opportunity for other symptoms to be added by participants. • The prevalence scale assesses the presence or absence of symptoms (Yes/No). • The other symptom dimensions are rated on a 0–10 NRS anchored by descriptors. For example, patients rate distress from none to very much; severity from none to very severe and frequency from never to constant. • The total score for each of these domains ranges from 0 to 320. Higher scores indicate greater symptom distress, severity, and frequency. • To calculate the total symptom burden score, all subscale scores (prevalence, distress, severity, and frequency) are summed and then multiplied by 0.1008 to report the total score out of 100.	This tool has the advantage of evaluating several dimensions of symptoms rather than just prevalence and severity. This may make it of interest to researchers looking to further explore symptom experience. However, it was developed and used in a relatively young and educated CKD 4–5 patient population. It has yet to be validated externally. Its relatively complexity makes it less likely to be clinically useful, especially for frail or cognitively compromised patients.
Leicester Uraemic Symptom Score (LUSS) [55]	• A self-report multidimensional tool that assesses the frequency and intrusiveness of 11 symptoms: itching, sleep disturbance, loss of appetite, excessive tiredness, pain in bones/joints, poor concentration/mental alertness, impotence/lack of sex drive, loss of muscle strength/power, shortness of breath, muscle spasm/stiffness, and restless legs. Space is given for patients to write and rate any additional symptoms. • Frequency is assessed using the following response options: "Never," "Less than once a week," "1–2 times a week," "Several times a week," and "Every day," scored from 0 to 4. • Intrusiveness is assessed with options of "Not applicable," "Not at all intrusive," "Slightly intrusive," "Quite intrusive," "Very intrusive," and "Extremely intrusive," scored from 0 to 5.	There is very little experience with the LUSS or evidence for validity. However, it appeared sensitive to change in CKD patients not on RRT during an exercise intervention study [55].
Kidney Dialysis Quality of Life-Short Form/SF-36 (KDQOL-SF) [56]	• A self-reported 36-item HRQL measure developed for CKD patients as a less burdensome version of the longer KDQOL questionnaire. • The tool focuses on three dimensions: (i) symptoms and problems, (ii) burden of kidney disease, and (iii) effects of kidney disease. • It includes two summary QOL scales, the physical (PCS) and mental (MCS) health summary scales, that are derived from the generic QOL tool - the Short-Form-12 (SF-12). • Scores range from 0 to 100 for each dimension with higher scores indicating better QOL.	Takes approximately 30 min to complete in healthier individuals but typically requires interviewer assistance and more time in elderly, frail patients. It provides comprehensive QOL information but is more suited to a research environment where dedicated staff can help with the administration and complex scoring. Not suitable for regular, routine screening and assessment or use in patients who are preterminal.
CHOICE Health Experience Questionnaire (CHEQ) [57]	• Self-reported 83-item QOL tool that was designed to complement the generic SF-36 (in a fashion similar to the KDQOL). • It incorporates an assessment of symptoms as 1 of 13 dimensions: (i) freedom, (ii) travel restrictions, (iii) cognitive functioning, (iv) financial, (v) restrictions on diet and fluids, (vi) recreation, (vii) work, (viii) body image, (ix) symptoms, (x) sleep, (xi) sexual functioning, (xii) access-related problems, and (xiii) QOL. • Scores range from 0 to 100, with higher scores indicating better QOL.	Requires approximately 30 min to complete in healthier individuals but typically requires interviewer assistance and takes longer in elderly, frail patients. It provides comprehensive HRQL information but is more suited to a research environment where dedicated staff can help with the administration and complex scoring. Not suitable for regular, routine screening, and assessment or use in patients who are preterminal.

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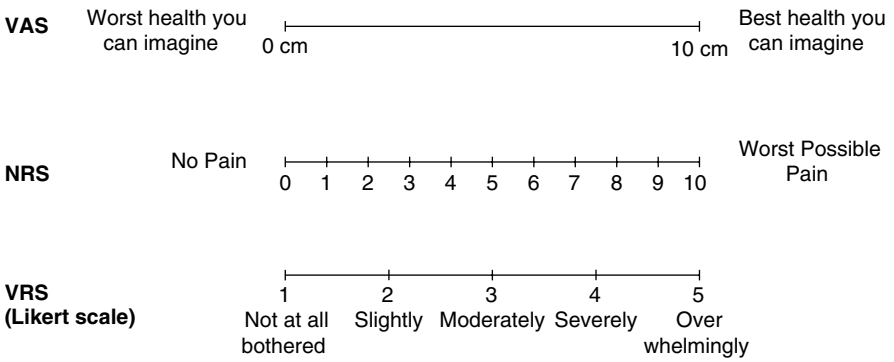

Figure 52.3 Examples of different formats for assessing symptom severity.

Table 52.4 Fundamental aspects of symptom management.

The symptom experience is subjective and multifactorial in nature. Factors including gender, ethnicity, age, and disease severity may contribute to reported symptomatology.
• **Acknowledge the symptom and validate the patient's suffering, as this is an important part of the therapeutic intervention.**
The aim of treatment is to ameliorate symptoms that are burdensome and impact negatively on the patient's QOL. It is not always necessary or possible to resolve them completely.
• **Negotiate with the patient an acceptable level of symptom control.**
Many symptoms are synergistic and interrelated, and not all symptoms will need to be addressed independently.
• **Determine if one symptom is likely the root cause of other symptoms to help focus therapy.**
Use a three-step approach to symptom management.
1) **Rule out and address contributing factors.**
2) **Maximize the use of nonpharmacological interventions.**
3) **Consider pharmacological interventions if symptoms continue to impact adversely on the patient's QOL.**

factors, (ii) maximizing the use of nonpharmacological interventions, and finally (iii) considering pharmacological interventions if symptoms continue to impact adversely the patient's QOL. Nonpharmacologic therapies have become a vital part of symptom management. They may be used successfully as stand-alone therapies but are also often required to augment pharmacologic treatment to achieve adequate relief (i.e. multimodal therapy). This approach not only maximizes health outcomes, including patient safety, but also aligns with most patients' treatment preferences. Some patients express frustration with taking multiple medications and realize that medication is not always the best strategy [22]. Many are interested in nonpharmacological approaches to relieve symptom burden. Optimal patient outcomes often require multiple approaches utilized in concert, coordinated via a multidisciplinary team.

Conclusion

Symptom screening, assessment, and management should be integrated into routine nephrology care for all patients with CKD to improve patient wellbeing and QOL. This is consistent with KDIGO recommendations that state "Symptom assessment and management is an integral component of quality care for patients with advanced CKD. Regular global symptom screening using validated tools such as the ESAS-r:R and POS-renal should be incorporated into routine clinical practice." As the number of patients with CKD rises, it will become increasingly important to direct patient care services and research toward symptom management. There is a critical need for innovation in this area: better insight into the pathophysiological processes is required to inform clinical management and improve patient QOL.

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53

Prognostication in Advanced Chronic Kidney Disease

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Introduction

Prognostication is a critical component of the care of patients with advanced chronic kidney disease (CKD). Maintenance dialysis in patients with end-stage kidney disease (ESKD) can prolong life and may ameliorate uremic symptoms, and yet annual mortality remains close to 17% [1] and many continue to suffer a high symptom burden even on dialysis [2]. The decision to commence dialysis is complex and relies on patient preferences and past experiences, the nephrologist–patient relationship as well as regional and cultural factors. Ideally, conversations about whether to start dialysis occur in the outpatient setting, with sufficient education and involvement of family. Yet a third of patients begin dialysis with little or no pre-ESKD care, thus without the opportunity for optimal planning [1]. Since dialysis requires frequent procedures that disrupt daily routines, often including travel to appointments, the impact of dialysis extends beyond the patient to the family and caregivers. Discussion of dialysis initiation ought to include a weighing of the burden of dialysis against time gained and other benefits to dialysis. These efforts would be consistent with society guidelines and recommendations to include prognosis sharing in decision-making [3, 4]. Key to this discussion is the prognosis of the patient with and without dialysis. While we lack randomized clinical trials on life expectancy with comprehensive conservative kidney management compared to dialysis with supportive care, observational studies suggest that, in older adults, time gained by choosing dialysis is divided into time spent receiving treatment or in hospital, with a smaller fraction of time at home [5]. Prognosis of patients' quality of life and functional status with and without dialysis would be of value to patients yet even less data is available in this area.

Goals of Prognostication

Prognosis is the likely course of the disease and its impact. In discussing prognosis with patients, the outcome of interest is often survival. This chapter focuses on prognostication with short-term mortality as the goal, given the context of kidney supportive care. Clinicians, patients, and families may also be interested in prognostication of functional status, symptom burden, quality of life, hospitalizations, place of death, and capabilities [6–8].

The immediate goal of prognostication is to share information with the patient and family. Only once the patient is aware of their prognosis can they adequately plan for their future and make decisions. In this way, discussing prognosis may assist the clinician and patient in shared decision-making. In certain circumstances, some patients may defer disclosure of prognosis to family or caregivers, who ultimately will benefit from sharing of prognosis. Prognosis sharing may help patients and families prepare and accept the disease trajectory. This in turn may facilitate planning and empowerment of treatment decisions. Therefore, prognostication has a role in shared decision-making such that it can reduce regret or discordant treatment plans. Prognostication must recur as the status of the patient shifts with accumulation of deficits such as in frailty or following intercurrent illness or hospitalization to provide opportunities for amending the care plan (Figure 53.1).

Prognostication may also improve identification of high-risk patients and thus facilitate access to kidney supportive care and comprehensive conservative care for these patients and, if appropriate, the discussion of withdrawal of dialysis and the organization of a timely transition to hospice [8].

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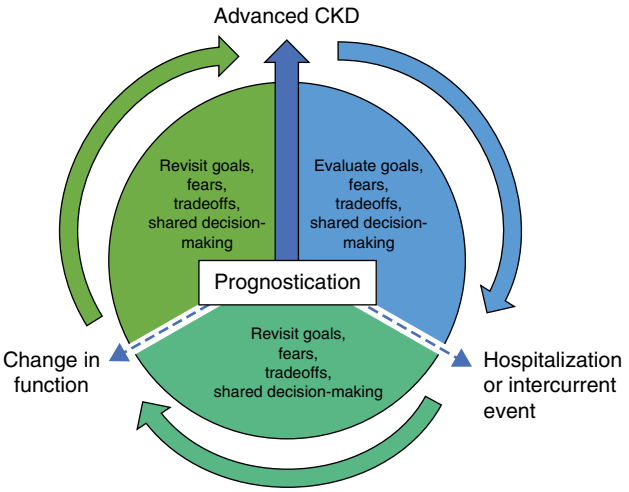

Figure 53.1 Prognostication framing and reframing goals of care discussions in kidney supportive care.

Patients' Preferences on Prognostication

Evidence suggests patients with ESKD wish to receive prognostic information from their nephrologist unprompted [9, 10]. In a Canadian study of 584 CKD and ESKD patients, the vast majority (90.6%) reported it was somewhat or extremely important to be informed about prognosis. Patients in this study overwhelming wanted detailed information about their medical condition and knowledge of treatment options, including withdrawal from dialysis. They also wanted to be prepared and able to plan ahead in the case of death. Yet, in this sample, only 5.6% rated being well informed about their condition [9]. In a qualitative study of US hemodialysis (HD) patients, only 10% reported discussing prognosis and 13% reported discussing end of life with nephrologists, but 80% expressed an interest in having end-of-life discussions [11]. A study of Canadian nephrologists found less than half reported always or often discussing estimated survival in patients who had ESKD [12]. Prognostic information must be presented in the appropriate context. [13] In a qualitative study of US patients, patients reported feeling "shut-down" by nephrologists when they asked about the implications of dialysis for their quality of life and prognosis [11]. In the absence of receiving prognostic information, patients use their own sense of prognosis to inform their decisions. In a US hemodialysis study of 207 patients, none reported receiving prognostic information from their nephrologist. Among these patients, those who felt they had a greater than 90% chance of being alive at 1 year were significantly more likely to prefer life-prolonging measures [11–13]. In summary, patients use prognostic information to make decisions and poor communication about prognosis may lead to difficulty in the patient–physician relationship. Thus, an additional benefit of prognostication may be that truth-telling is an opportunity to build rapport with patients.

Understanding Prognostic Models

Several prognostic models exist to predict short-term mortality in patients receiving dialysis. To identify the most appropriate model to use, it is important to determine the applicability to the desired population. An astute user of prognostic models will want to understand the population from which the model was derived. Did the model include only elderly patients or not? Was the model based on registry data, which might only include patients referred to a nephrologist or a population-based database, which might include all patients in a particular region? Did the model include incident dialysis patients, for whom the decision had already been made that they were appropriate for dialysis, or incident CKD 5 patients regardless of decision to initiate dialysis? Were prevalent patients included in the model? What end-point was chosen (determinants of outcome at 3 months vs. 2 years)? How was the population defined and is this applicable to your patient considering regional differences, recruitment policy, and cultural context?

Prognostic models are evaluated based on discrimination and calibration, and ideally are externally validated in a population different from the one from which it was derived. The Concordance statistic (c-statistic) is a measure of discrimination that summarizes how well a prognostic model differentiates between patients who died and survived at a particular follow-up time. A value of 0.5 for the c-statistic reflects that a model is no better than flipping a coin, while a perfect model would have a c-statistic of 1.0. Calibration reflects how well the predicted probability of survival based on a prognostic model compares to the actual survival outcomes.

There are limits to the use of prognostic models in the context of kidney supportive care. First, prognostic tools should not be used as if they can predict the future course of a given patient with complete certainty, nor as means to withhold treatment. Prognostic tools are best used with an appreciation of the uncertainty of the course of ESKD, in the context of balancing of patient and family preferences with reasonable expectations. Finally, in the application of a prognostic model to a particular patient, the population from which the model was derived and the limitations of that model must be considered. Table 53.1 summarizes suggested uses and contraindicated uses for prognostic models.

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Table 53.1 Use of prognostic models in kidney supportive care.

Suggested uses	Contraindicated uses
To aid in shared decision-making with patient and family	To deny a treatment
To respond to patient's request for information on prognosis	To make recommendations in a population that was not tested or validated by the model
To identify high-risk patients who may not benefit from dialysis	To irreversibly categorize a patient without appreciating the possibility of change in status
To identify high-risk patients who may benefit from early supportive care	To make decisions in isolation of clinical context
To organize heath supply by estimating needs	

Availability of the Evidence on Prognostic Models in the Context of Kidney Supportive Care

Current prognostic models for patients with ESKD typically use mortality as the outcome. Predictors of mortality are generally identified from the literature and tested for independent association with the outcome. Most prognostic models in use for ESKD include a combination of age and comorbid conditions, and occasionally information about functional status, laboratory data, clinician assessment or patient trajectory. Earlier research identified the modified Charlson Comorbidity Index was able to predict mortality [14–16], however it did not perform as well in an older cohort [17]. Age is a strong predictor of mortality and is included in several prognostic models. The relationship between age and mortality is influenced by degree of independence (Figure 53.2), such that mortality is greater at a given age if the functional status score is lower [18]. Functional status is an important independent predictor of mortality in ESKD. In the Dialysis Outcomes and Practice Patterns Study of 12 countries and 7226 hemodialysis patients, a low functional status score had more than two-fold the risk of death at 17 months follow-up compared to those with who were functionally independent [18]. Table 53.2 summarizes current prognostic models for ESKD, including scores and multivariable models. Several models are derived from incident dialysis patients in registry data and a few focused specifically on elderly patients. Overall, the discrimination of these models is fair. External validation is limited to a small number of models and generally demonstrates a lower discrimination than the original cohort.

Some prognosis tools were developed in patients with CKD not yet on renal replacement therapy. They often focused on middle-term outcome (2–4 years) or an earlier stage of CKD, which is outside of our scope. One recent tool was developed for a population with severely decreased glomerular filtration rate [29].

Reasons for low or fair discrimination among current prognostic models are multifactorial. External validation performed retrospectively may have relied on operationalized predictors for available data, diminishing the strength of association of those variables [17]. Models derived from one country may not be applicable to another if practice patterns that differ among countries also associate with mortality and are not included in the model. Other tools did not perform well in external cohorts possibly because the external validation included some of the original cohort, which might have falsely elevated the discrimination of the original cohort [25]. The overall low performance of current models may also be due to failure to capture the illness trajectory by using only one time point.

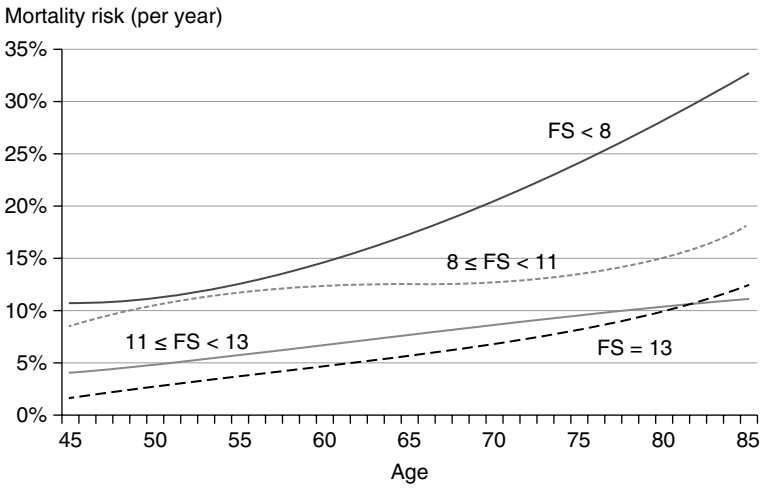

Figure 53.2 Mortality risk by age and functional status (FS) score. *Source:* Jassal et al. [18]. © 2016 Elsevier.

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Table 53.2 Comparison of prognostic tools for short-term mortality in ESKD.

Source	Type	Population	Sample	Outcome and follow-up time	Predictors in the score/model (weighted points in score)	Characteristics
Canada [19]	Retrospective	Population based; incident dialysis patients from 2003 to 2012	2199 adults age ≥65 years	17% died at 6 months	6-month score: age ≥80 (2), eGFR (1–3), hospitalization in prior 6 months (2), atrial fibrillation (2), chronic heart failure (2), metastatic cancer (3), lymphoma (5)	Validation cohort c-statistic was 0.72 Good calibration No external validation cohort
France [20]	Retrospective	Registry of all treated ESRD patients; incident dialysis patients from 2002 to 2006	2500 adults age ≥75 years in development cohort; 1642 similar adults in validation cohort	19% died at 6 months	6-month score: low body mass index (BMI) (2), diabetes (1), congestive heart failure stage III–IV (2), peripheral vascular disease (PVD) stage III–IV (2), dysrhythmia (1), active malignancy (1), severe behavioral disorder (2), impaired mobility (3), unplanned dialysis (2)	Validation cohort c-statistic was 0.70 External validation exists on adapted criteria: US <0.70 [17], Spain 0.68 [21]
France [22]	Retrospective	Registry of all treated ESRD patients; incident dialysis patients from 2005 to 2012	12 500 adults ≥75 years in development cohort; 11 848 in validation cohort	10.5% died at 3 months	3-month score: male gender (1); age (0–3); congestive heart failure (2–4); severe PVD (1); dysrhythmia (1); severe behavioral disorders (2); active malignancy (2); serum albumin (2–5); impaired mobility (4–9)	Validation cohort c-statistic was 0.75. Validation in a more recent cohort: c-statistic 0.79. External validation exists: Belgium cohort: c-statistic 0.74 [23]
United States [24]	Retrospective	Registry of treated ESRD; incident dialysis patients from 2009 to 2010	52 796 adults age ≥67 years in development cohort; 16 645 similar adults in validation cohort	12% died at 3 months; 20.3% died at 6 months	6-month score: age (0–3 points), low albumin level (1), assistance with daily living (1), nursing home residence (1), cancer (1), heart failure (1), hospitalization (1)	Validation cohort c-statistic was 0.69–0.72
United States [25]	Prospective	Prevalent dialysis patients from Fresenius dialysis units from 2006 to 2008	512 adults in development cohort; 514 adults in validation cohort	24% died at 6 months	6-month multivariable model: surprise question (not surprised if patient died in 6 months), serum albumin, age, peripheral vascular disease, dementia	Validation cohort (included some derivation cohort participants): c-statistic 0.80 External validation (Canadian cohort c-statistic 0.70 but poor calibration) [26]
Finland [27]	Retrospective	Registry of treated ESRD; incident dialysis patients from 2000 to 2008 for development and 2009–2012 for validation cohort	4 335 adults ≥18 years in development cohort; 1 768 in validation cohort	13.8% died at 1 year and 24.9% died at 2 years in development cohort 11.1% and 21.2% died at 1 and 2 years in validation cohort	1-year multivariable model: phosphorus, C-reactive protein (CRP), heart failure, peripheral vascular disease, age at start of renal replacement therapy (RRT), ESKD diagnosis, serum albumin	Validation cohort (2009–2012 registry data) c-statistic: 0.74 Suboptimal calibration with overestimating death risks in the validation group
Europe [28]	Retrospective	AROii database and DOPPS III were used for development and validation cohorts, respectively	11 508 incident hemodialysis patients in development cohort; 10 615 in validation cohort Mean age 64 years	10.9% and 9.4% died at 1 and 2 years	1-year score: calcium (0–3), creatinine (0–2), serum albumin (0–3), CRP (0–5), ferritin (−1 to 1), hemoglobin (−1 to 2), actual blood flow (−1 to 1), vascular access (0–2), BMI (−1 to 2), CV history (0–2), cancer history (0–4), age (−5 to 6 points)	Validated externally using DOPPS data c-statistic 0.71

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Other variables that are not easily identified retrospectively, such as functional status, could improve discrimination [8, 17].

There is a need for prognostic information about the quality of their life and other patient-related outcomes in advanced kidney disease, however little data exists outside of prognostic models for mortality. A Dutch study of 80 dialysis patients created a risk score including a high case complexity score (INTERMED), age, and diabetes [30]. The INTERMED score includes biological, psychological, social, and healthcare domains to produce a score indicating the degree of care needs. Although not yet externally validated, this model was able to detect patients at risk of poor physical and mental quality of life scores, as well as low 1-year survival [30].

Limitations and Future Research Directions

Challenges exist in the current prognostic models. For the clinician seeking prognostic information for patients not yet on dialysis, greater study of population-based cohorts is needed. Many of the available models have not been rigorously tested in external cohorts, and discrimination is generally only fair. Opportunities exist to study novel markers, both at baseline and over time, to determine if this can improve prognostication. Given the mediocre discriminatory power of current models, nephrologists should not use these models to define a patient's treatment options, but rather to inform the discussion of prognosis with patients. Further study is needed to define the patient-reported outcomes most appropriate for future model development, and patients should be involved in future model building to define patient-centered cut-points and to inform the practice of using and integrating these models.

Studies allowing better definition of the spectrum of changes in symptom burden, quality of life, and physical performance are expected. An US study of 32 incident patients starting dialysis found that a composite measure of symptom burden did not change with dialysis initiation [31]. A UK study of conservatively managed patients with stage 5 CKD demonstrated that while average symptom burden increases in the final months of life, individual patterns may vary, making prediction of symptom burden difficult (Figure 53.3) [32]. A Canadian study including 261 HD prevalent patients indicated that change in symptom burden is associated with change in mental and physical health composite [33]. Low functional status is an important outcome in patients receiving maintenance dialysis. For example, two systematic reviews have shown the association of geriatric impairments like frailty, malnutrition, depression or performance status with higher risk of hospitalization in ESKD [34, 35]. Among nursing home residents who initiated dialysis, 58% had died and only 13% maintained their functional status at 1-year follow-up [36]. Among stage 5 CKD patients receiving conservative kidney management in the UK, functional status was fairly stable in the year preceding death but declined in the last month [37] (Figure 53.4). In the US study of 32 incident patients, they found that though patients' self-reported physical functioning may improve following dialysis initiation, objective physical performance does not increase in parallel. In summary, the available data suggests that symptom burden in advanced CKD and ESKD is high, may not improve with dialysis, and increases with time, but interindividual variation is high. Functional status may be more stable until the final month in those receiving

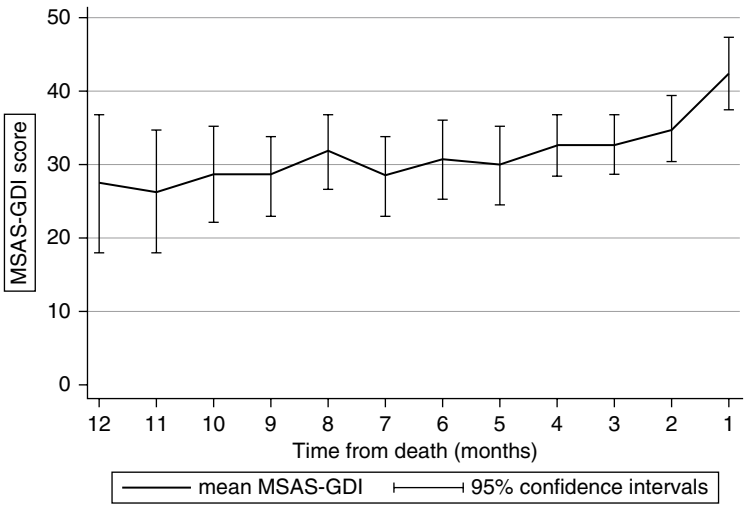

Figure 53.3 Trajectories of symptoms using the Memorial Symptom Assessment Score (MSAS) in patients with stage 5 CKD in the months preceding death. *Source:* Murtagh et al. [32]. © 2011 American Society of Nephrology.

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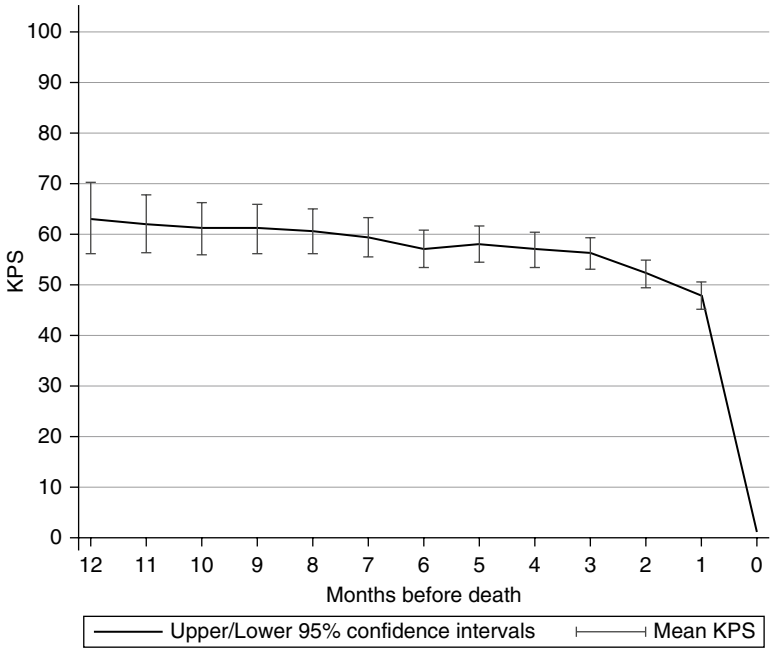

Figure 53.4 Trajectory of mean Karnofsky Performance Scale (KPS) score over the last year of life among conservatively managed stage 5 CKD patients who died. *Source:* Murtagh et al. [37]. © 2011 John Wiley & Sons.

conservative kidney management as opposed to dialysis, but this may depend on the functional status at time of dialysis initiation. Greater study of these patient-centered outcomes is urgently needed.

Excellent communication around prognosis sharing is critical to shared decision-making and nephrologists can enhance their comfort level in communicating prognosis through skill-based training [38, 39]. Further study of how to best disseminate communications skills to nephrologists is needed. Finally, we need greater research on the impact of using prognostic models within a health system, for example whether prognostic models can identify patients who most urgently need advance care planning or supportive care resources.

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54

Advance Care Planning

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Introduction

A 75-year-old woman has end-stage kidney disease (ESKD) secondary to ischemic nephrosclerosis. She commences hemodialysis. Over time, it becomes apparent that she is developing significant cognitive impairment. The dialysis nurses struggle to deal with her behavioral problems. There is uncertainty within the family and among her clinicians as to whether to continue dialysis. No plan was made or discussed by the nephrologist while the patient was still competent to address her care in anticipation of worsening cognitive impairment. To the best knowledge of the family, the patient never expressed her wishes in the event of incompetence or clinical deterioration.

Advance care planning (ACP) is a message to the future. It is a process of discussion and planning by a competent person, addressed to their future clinicians, expressing their wishes and values in the event of becoming incompetent. Necessarily, it is highly personal. It holds the weight of law and is enforceable, except where it requests an illegal or medically unreasonable act.

The absence of ACP is silence. At the very moment where both clinicians and families struggle with medical decision-making, no one knows the expressed wishes of the patient. Apart from the patient him- or herself, any other decision-maker stands at a metaphorical distance and can, at best, only surmise the wishes of the person, but they cannot truly know. The presence of an advance care plan allows the voice of the person to be heard. That voice is significant and will, ideally, guide both the clinician and the family in acting in the best interests of the patient. Unfortunately, in the context of nephrology the opposite often occurs, where patients have not discussed end-of-life care, have not completed an advance care plan, and die receiving intensive therapies that may be inconsistent with their wishes [1, 2].

The idea of advance directives, the antecedent of ACP, was founded on two principles: the ethical principle of autonomy and the legal principle that patients should not be subject to treatment without their consent. The role of ACP has been acknowledged in nephrology for several decades [3, 4]. Nevertheless, significant deficits in understanding, uptake, and research remain. Many nephrologists do not understand the precise role and process of ACP and many feel unprepared in end-of-life decision making, including undertaking ACP [5]. Globally, the uptake of ACP by nephrologists varies considerably [6, 7]. The level of evidence for the timing, content, comprehension, acceptability, and ultimate effect of ACP on clinical outcomes in nephrology is limited (Table 54.1).

The Nomenclature of Future Care Plans

In any discussion about future care planning, language is a complicating factor. There are multiple forms of future plans for medical care. Table 54.2 summarizes the definitions of commonly used terms. These definitions are important for clear communication. The law views each term discretely in terms of objective, scope, content, and enforceability. Two main types of instruments exist: *instructional*, where the person specifies their preferences in medical care, and *proxy*, where the person nominates a surrogate decision-maker. The person may combine these approaches in one document. There are significant overlaps in these definitions. In nephrology literature, the most commonly used term is ACP.

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Table 54.1 ACP for patients with ESKD: a summary of evidence and practice recommendations.

Treatment	Recommendation	Certainty of evidence	Strength of recommendation
ACP	We suggest that ACP is an integral part of kidney care	Weak	Low
	We suggest that ACP fosters hope rather than the reverse	Weak	Moderate
	We suggest that ACP of patients with ESKD leads to improved bereavement outcome for caregivers, such as reduced anxiety, depression, and post-traumatic stress disorder	Weak–moderate	Moderate
	We suggest that, as a minimum, ACP should be conducted on patients with chronic kidney disease who have a limited prognosis as evidenced by the surprise question and all patients with ESKD on conservative (nondialysis) kidney management	Weak	Low
	We suggest that nephrologists should initiate and sign off on advance care plans	Weak	Low

ACP, advance care planning; ESKD, end-stage kidney disease.

Table 54.2 The nomenclature of future planning.

Advance care plan

An advance care plan is the end result of a process of advance care planning whereby a competent person plans for future health and personal care when they are incompetent by making their values, beliefs, and preferences known.

Advance directive

An advance directive is a type of advance care plan that is written and signed by a competent adult and recognized by the law. It can record the person's preferences for future care and can appoint a substitute decision-maker to make decisions about healthcare and personal life management. It is activated when the person becomes incompetent. To be valid, an advance directive must meet the local legal requirements of that jurisdiction.

Living will

A living will is another term for an advance directive. Many jurisdictions have living will statutes.

Advance statement

The provision of a UK statute. A statement of wishes and preferences made by a competent person for future medical care in the event the person becomes incompetent.

Advance decision to refuse treatment

The provision of a UK statute. Refers to a specific refusal of treatment in a predefined future medical situation.

Healthcare proxy form

A healthcare proxy form is a legal document that allows a person to choose a surrogate decision-maker, a person to make medical decisions on their behalf when they are incompetent. In some jurisdictions the person who is authorized may be called a "proxy", in others the person may be called an "agent".

Durable power of attorney for healthcare

A competent person may nominate another individual to make healthcare decisions when the principal is incompetent. In the UK, the equivalent is the *lasting power of attorney* and in some Australian jurisdictions, an *enduring guardian*.

Physician orders for life-sustaining treatment

Physician orders for life-sustaining treatment are physician orders for seriously ill patients that guide treatment regarding cardiopulmonary resuscitation, extent of medical treatment and artificial nutrition.

Current Uptake of ACP

> *It is time to stop discussing the need for [Advance Care Planning in nephrology] and to start exploring ways to make it work. . . it is time for nephrologists to assume responsibility for this aspect of dialysis care*
>
> *Source: Holley and Davison [8].*

The uptake of completed advance care plans in patients with CKD is unknown. Studies reveal that the numbers of patients with ESKD who have completed an advance directive (AD) varies considerably, ranging from 6% to 51% [6, 9]. In a nationwide survey of renal clinicians in Australia, 62% of respondents reported that ACP was conducted in their primary workplace "never or hardly ever" or "some of the time" only. Less than one-third reported undertaking

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ACP with a majority of their patients and nearly two-thirds of the respondents felt that ACP was performed "poorly" or "very poorly" [10].

Role of ACP in Nephrology

The role of ACP in nephrology may be illustrated by the following brief case vignettes.

Case 54.1

A 79-year-old man has type II diabetes mellitus and hypertension. Over time he has worsening kidney function. Eventually, he commences dialysis. There are several complications in the first 3 months, including a struggle to come in to the dialysis center on some days, great fatigue, complications of vascular access, sepsis, and herpes zoster. Several months later he collapses at home. Physical examination reveals he has an ischemic right foot. Imaging shows an intracerebral hemorrhage. He is due to have dialysis that day. At a family conference, the nephrologist recommends stopping dialysis and providing end-of-life care. The family is divided as to whether to continue with dialysis or not. During these discussions, the following interchange occurs:

Doctor: "Does your father have an advance care plan?"

Son: "No."

Doctor: "Did he ever talk about what he would want to happen if he became very ill?"

Son: "No…in our family we wouldn't talk about those things. But doctor, did you talk about this with him?"

Doctor: "No, we never got around to it…"

Case 54.2

An 82-year-old man with ESKD is on peritoneal dialysis. He discusses future plans with his nephrologist and an advance care plan is made. Later, he has a major myocardial infarction resulting in cardiogenic shock requiring inotropes. The advance care plan guides the clinicians and family to comply with the wishes of the patient in withdrawing dialysis and inotropes, and providing end-of-life care.

These cases illustrate the utility of ACP when it has occurred and the difficulties that arise when it has not. In the general population, advance care plans have been shown to increase agreement in patient and family members about end-of-life wishes [11], reduce family distress, reduce the use of unwanted life sustaining procedures prior to death, and provide care that is more consistent with the wishes of the patient [12].

The modern epidemiology of ESKD, with its striking combination of advanced age and significant comorbidity, enhances both the relevance and utility of ACP in nephrology. In developed nations, the most prevalent age cohort of dialysis patients is the 65–84-year-old group [13]. In the United States, patients 75 years and over are the fastest growing group of dialysis patients [14]. The prevalence of comorbidities in this cohort, particularly type II diabetes mellitus and cardiovascular disease, reduces overall prognosis. Indeed, the annual mortality of dialysis patients 75 years and older is approximately 25% [13]. It is precisely this cohort that is most likely to experience a sudden, critical deterioration, at which time a completed advance care plan would be extremely useful. Dialysis patients, however, are "typically unprepared for end of life" [15].

The potential utility of advance care plans is highlighted by the common circumstances surrounding dialysis withdrawal. Approximately 15–29% of the deaths of dialysis patients occurs after a decision to withdraw from dialysis [14], yet most dialysis patients report never having had a conversation with their nephrologist about the circumstances under which they would consider withdrawal [4]. An advance care plan prompts such a discussion and gives the patient a voice in what can otherwise be a vexed decision about the scope of care of a patient with ESKD. An advance care plan permits the person to establish limits to their care and guides the clinician and family.

Authoritative Recommendations for ACP in Nephrology

Within the discipline of nephrology, there are several authoritative recommendations and guidelines on advance care plans, which are set out in Table 54.3.

Barriers to Completion of Advance Care Plans

There are many barriers to advance care plan completion. In Table 54.4 these are divided into issues for physicians, patients and families, and medical systems.

One of the enduring myths about advance care plans is that they extinguish hope. Hope is intrinsic to us as human beings. Hope is our imagined future. Davison and Simpson conducted a qualitative study with interviews of dialysis patients who had completed an advance care plan [27]. They found that providing realistic information and a discussion about the future does not destroy hope. Indeed, such discussions enhanced a sense of hope "by providing information early in the illness that focuses on the impact

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Table 54.3 Guidelines and recommendations for advance care planning in nephrology.

Kidney Disease: Improving Global Outcome (KDIGO) Controversies Conference on Supportive Care in CKD [16]
"The treating nephrology team should engage in advance care planning. These discussions should start early in the disease trajectory and should include discussions about health states in which patients would want to withhold or withdrawal from dialysis."
Renal Physicians Association (USA)
Clinical Practice Guidelines on Shared Decision-Making in the Appropriate Initiation of and Withdrawal from Dialysis [17]
"For dialysis patients, the interdisciplinary renal care team should encourage patient-family discussion and advance care planning and include advance care planning in the overall plan of care for each individual patient." "At a minimum, each dialysis patient should be asked to designate a legal agent. . ." "Patients with decision-making capacity should be strongly encouraged to talk to their legal agents to ensure that the legal agent knows the patient's wishes and agrees to make decisions according to these wishes." "Advance directives should be honored by dialysis centers [and] nephrologists. . . except possibly in situations in which the advance directive requests treatment contrary to the standard of care."
Australian and New Zealand Society of Nephrology (ANZSN**)**
Position Statement on Renal Supportive Care [18]
"Advance care planning should be available to all patients with CKD including ESKD on renal replacement therapy. Advance care planning is a process of patient-centered discussion, ideally involving family/significant others, to assist the patient to understand how their illness might affect them, identify their goals and establish how medical treatment might help them to achieve these."
"An Advance Care Plan is only one useful outcome from the Advance Care Planning process, the education of patient and family around prognosis and treatment options is likely to be beneficial whether or not a plan is written or the individual loses decision-making capacity at the end of life."
"Facilitating Advance Care Planning discussions requires an understanding of their purpose and communication skills that need to be taught. Advance Care Planning needs to be supported by effective systems to enable the discussions and any resulting Plans to be used to aid subsequent decision-making."
The End Stage Renal Disease Workgroup on End-of-Life Care (USA)
Recommendations to the Field [19]
This group recommended dialysis units facilitate advance care planning and that nephrology healthcare professionals "routinely invite patients to express their end-of-life care preferences in the required semi-annual short-term and annual long-term care planning meetings. . .. Encourage patients to communicate their preferences to family and to complete written advance directives."
UK Department of Health
Getting it Right: End of Life Care in Advanced Kidney Disease [20]
This document recommended that all dialysis patients be offered ACP. It stated that "ACP could take more than one discussion with a patient and that for some patients the discussion may take some time and may require revisiting at a future date. If possible involve families and carers in these discussions."

on daily life, empowering patients and enhancing relationships with staff and loved ones" [27]. When the opposite occurred ". . .unaddressed fears about the future and a lack of preparation of what lay up ahead were constant threats to hope" [27].

Threshold Issues

Prior to embarking on ACP in CKD patients, several general points should be considered. The first is that ACP would benefit all patients with complex, chronic diseases. Indeed, most older patients with CKD will die before reaching the need for dialysis or conversations around conservative kidney management (CKM). The second is issue is timing. Most countries emphasize the importance of early discussions which help to normalize the process. Other issues include the following:

Which CKD patients should commence advance care planning?

This is an open question and responses lie on a spectrum. At one end is a recommendation by the US Renal Physicians Association that ACP should be included in the overall plan of care for all chronic dialysis patients [17]. Another response is to concentrate on those patients with a limited prognosis, as evidenced by such factors as advanced age, high comorbidities, poor performance status, frailty, and the use of the surprise question ("Would you be surprised if this patient died in the next year?"). The argument for a focus on this cohort is that they are more likely to present with major sentinel events where an advance care plan would be very useful. The other cohort of patients who will uniformly benefit from an advance care plan are those on a conservative, nondialysis pathway, i.e. CKM [30].

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Table 54.4 Barriers to ACP in nephrology.

Physician barriers[a]
• Lack of training in these discussions [5, 21]
• Discomfort in discussing resuscitation [22]
• Time constraints [21]
• Uncertainty as when to raise a discussion about future plans [23]
• Lack of understanding of what palliative care/a palliative or supportive care approach would involve [24]
• Belief that an ACP discussion will destroy hope [21]
• Uncertainty about the law [25, 26]
• Belief that patients/families do not want these discussions [24]
• Thought to be too emotionally draining
Patient and family barriers
• Inadequate understanding of ACP [21]
• Belief that it is the nephrologist's responsibility to raise the subject [27]
• Perception that advance care plans are a mechanism to permit premature medical abandonment or precipitate death [28]
• Reluctance to think about or discuss death
• View that advance care plans are unnecessary because one's family "will know what to do when the time comes"
• Belief that wishes contained in an advance care plan will not be followed
• May not be aware of the serious nature of their illness
System barriers
• Inadequate resources and financial support for training and administration [10]
• Incomplete distribution of advance care plan to all clinicians

[a] This table is based, in part, on similar lists devised by Davison [29] and Brown [30]. Their work is acknowledged.

The culture of the patient is also important to consider. The Western emphasis on individual choice and autonomy may not be appropriate in cultures where decisions, such as future planning, are not made by the individual but by the family as a collective [31]. In some religions it is considered inappropriate for an individual to pre-empt divine will in any future scenario.

When should an advance care plan be raised?

> *It is unacceptable to leave patients and their families dangling in the throes of a progressively debilitating disease wrought with . . . difficult medical decision making that often goes unguided by health care providers* [32].
>
> *Source: Jean Holley and Sara Davison, Nephrologists.*

The timing of an advance care plan is often an unresolved issue that sits between the nephrologist and the patient. The patient tends to wait for the subject of future planning to be raised and the nephrologist is uncertain when to raise it. This paralysis in communication leads to silence and both parties drift into an uncertain clinical future. There is "no universally accepted framework to evaluate either a patient's readiness to engage in ACP or the outcomes of ACP" [32]. Schell and Lam recommended regularly asking patients about their experience of dialysis, which may prompt an open discussion about the goals of care [33]. This basic act of courtesy and curiosity may be all that is needed to open a broader conversation.

Who should participate in these discussions?
Dialysis patients have expressed a preference that their family are present at an ACP discussion [34]. All recommendations advise including the patient, the family, and the surrogate decision-maker. This is logical and prudent. It is considered best practice that the family be aware of the person's decisions, including the detailed wishes of the patient and whom they have nominated as a surrogate decision-maker.

Which clinician(s) should initiate the process of ACP?
Ideally, nephrologists initiate this discussion [35]. Patients with CKD and their families concur [36]. That leaves open the participation of other members of the multidisciplinary

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team, including renal fellows, social workers, and nurses. As Brown stated, whatever the process or professional participation, "at the end of the day, nephrologists need to take final responsibility [for ACP] . . ." [30].

Legal Requirements

A critical issue for the preparation of a valid advance care plan is compliance with the law. There are two sources of law in relation to advance care plans. The first is statutes passed by legislatures. The second is common law (judgments of the courts). The former introduces its own complexity, as each statute may be subtly different. Nevertheless, there are some universal principles uniting both common and statutory law in relation to advance care plans. First, the law requires that the person is competent at the time of completion of an advance care plan. This implies that the nephrologist is satisfied clinically that the person had the requisite elements of competence (capacity), including understanding, retaining the information, and reasoning toward a conclusion. This is a significant point given the increasing evidence that patients with ESKD suffer cognitive impairment prior to and during dialysis [37]. The law assumes that a person was competent when they completed an advance care plan and also states that this presumption can be challenged. The second prerequisite for a valid advance care plan is that the person was not coerced at any stage in the preparation and completion of an advance care plan. Both competency and voluntariness are crucial.

ACP statutes, whether instructional or proxy in nature, vary considerably. If a statute applies in a state, province or nation, it is important that nephrologists understand the relevant local legal requirements as they prepare for and conduct ACP. For instance, some US statutes require a witness or a notary to witness a document and some statues set out precise forms to be completed. Advance care plans have legal force in most western countries. When family members of an incompetent patient have a view conflicting with the advance care plan/AD, ethics and/or legal services should be invited to assist.

When a person lacks capacity and has not nominated a surrogate decision maker, one must be designated. Many countries have laws regarding surrogacy but the rules for nominating this individual differ between countries and states.

What Are the Elements of a Good Advance Care Plan?

ACP is a slow and deliberate process that can constantly evolve with changes in the patient's life situation and preferences (Table 54.5). Important aspects of this process are as follows:

- ACP entails gathering detailed medical and personal information about a patient.
- Ideally, physicians should engage in ACP with each patient who has advanced CKD or is on dialysis. At a minimum, physicians must engage in ACP with patients who have limited life expectancy, such as those with multiple comorbidities, malnutrition, and frailty. A patient requires ACP if a physician responds "no" to the surprise question, which is "Would you be surprised if this patient dies in the next year?" [38].
- ACP can be initiated at the time of diagnosis of advanced CKD or ESKD, at a change in life situation (e.g. moving into a nursing home), at a patients' request, at the time of starting dialysis or during routine nephrology visits.
- Even in the absence of a prior relationship, empathetic communication with the patient helps in initiating ACP conversations. Indeed, embarking on the ACP process actually helps establish a good rapport and trust. Exploring patient values, preferences, fears, hopes, meaning of life, and expressions of empathy help with establishing such rapport, and assists with preparing for the ACP and delivering information according to patient's needs.
- Using emotional ques and direct questions, a physician should assess a patient's readiness to engage in ACP. Barriers to readiness may include personal beliefs, fatalism, and cultural beliefs. For example, in some Asian cultures it is a bad omen to talk about death. In South-East Asian cultures, it is normal to discuss prognostic information with families instead of patients. In Western cultures, it is considered ethical to seek permission from the patient and then discuss prognosis with families, with or without the patient [39].

Table 54.5 Elements of ACP.

1) ACP *can be* initiated at any time in a patient with CKD but *must be* completed in patients with a limited prognosis.
2) A nephrologist should gather medical and personal information (preferences, values, goals, etc.) for each patient undertaking ACP.
3) Use of excellent communication skills with expressions of empathy can help build trust and rapport with the patient.
4) Family members should be involved in the ACP process.
5) An ideal healthcare proxy is a person who can honor the patient's wishes when (s)he is unable to make decisions.
6) A shared decision- making model should be implemented while making end-of-life or dialysis initiation/withdrawal decisions.

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- It is good practice to involve family members, especially the likely healthcare proxy, in ACP decisions. This process can be emotionally meaningful for families [40]. Knowing a patient's wishes may help family members follow the patient's preferences about treatments such as dialysis should the patient not be competent to make decisions for himself or herself. Clinicians should clarify that the healthcare proxy understands and will be able to honor the patient's wishes. If these decisions are too burdensome or confusing for a nominated proxy, patients should be encouraged to designate someone else who is better able to handle decisions.
- Components of ACP that relate to life-sustaining treatments, such as dialysis, cardiopulmonary resuscitation (CPR), use of feeding tubes, and intubation, should include discussions about survival and quality of life. Several tools exist to guide such information: the Charlson comorbidity score [41], the prognostic model developed by Cohen et al. [42], the French Rein registry questionnaire [43], performances status [44], and the surprise question [38]. These prognostic tools are discussed further in Chapter 53.
- Decisions about CPR should be well informed. Large-scale studies have shown that most patients die during the same hospitalization after receiving CPR. Outcomes for older patients with CKD are particularly poor. In a large US-based study, the median survival after CPR was less than 5 months and the majority of the survivors were discharged to nursing homes [45, 46].

In ACP, it is ethically acceptable to make a recommendation based on the patient's life goals and then involve the patient in decision making, using appropriate communication skills. The decision should be documented in medical charts and other forms of documentation, such a living will, Ads, and healthcare proxy forms. A living will offers a detailed documentation of the patient's wishes, while ADs state end-of-life preferences more briefly [47].

What Evidence is there for the Effectiveness of ACP as an Intervention?

In the general population, ACP provides several benefits to patients and families. Completion of an advance care plan can result in improved quality of end-of-life care, fewer hospitalizations, less use of life-sustaining treatments, increased use of palliative care, hospice care, and death at the patient's preferred location [48, 49].

A limited number of ACP interventions have been studied in CKD patients. A pilot study of 27 seriously ill patients, including 10 patients receiving dialysis, showed that an hour-long patient-centered ACP interview reduced decisional conflict and enhanced satisfaction with ACP-related decisions [50]. When the same ACP intervention was studied in a larger number of patients with congestive heart failure and ESKD ($n = 313$ with 134 patients on dialysis), the results were similar between the ACP intervention and control groups for receipt of end-of-life care according to patients' preferences [51]. Another ACP intervention was the Sharing Patient's Illness Representations to Increase Trust (SPIRIT) intervention, a two-visit psychoeducational intervention that taught patients about their prognosis and clarified their wishes. This intervention resulted in enhanced patient-surrogate agreement on decisions and higher confidence of the surrogate decision maker in making decisions [52]. As an alternative to interventions by healthcare personnel, peer mentoring on ACP by other dialysis patients was shown to increase completion of ADs and enhance the wellbeing of dialysis patients, particularly African Americans [53].

ACP strengthens a patient's relationship with his(er) loved ones and helps them prepare for the future. In one study of ESKD patients, ACP also led to improved bereavement outcomes for caregivers, with reduced anxiety, depression, and post-traumatic stress disorder. If performed with sensitivity, ACP conversations can strengthen physicians' relationships with patients and families and improve physicians' wellbeing after a patient's death [54]. For a summary of findings of the current evidence on ACP see Table 54.6.

Importance of Good Communication in ACP

Patients with CKD depend on communication with their physicians to plan for their future. A communication intervention in African American patients was shown to enhance rates of completion of ACP documents [55]. However, physicians often avoid prognostic and ACP discussions because they lack skill in conducting difficult conversations, while patients are afraid that they may disrupt their relationship with their physician by asking probing questions about prognosis and expressing their preferences. Patients typically rate prognostic conversations with clinicians as unsatisfactory [56, 57]. Meaningful conversations earlier in the illness could help avoid such misunderstandings [58].

In the United States most nephrology trainees receive no communication skills training during fellowship, which leaves them uncomfortable in conducting goals of care or end-of-life discussions [59]. Most nephrology trainees have expressed a desire to improve their communication skills [59]. Knowledge of the Renal Physicians Association guidelines for estimating and discussing prognosis is

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Table 54.6 Summary of findings on the evidence base for ACP in nephrology.

Outcomes	Number of participants (no. of studies)	Certainty of evidence	Conclusion
Hope and ACP in CKD patients	19 (1)	Low	Advance care plans do not impair hope. Indeed, they positively enhanced a sense of the future.
ACP interventions in CKD patients	593 patients and 390 relative participants (eight studies: five RCTs, three non-RCT interventions)	Low–moderate	Evidence that ACP interventions improved: • patient's perceived quality of communication • congruence of dyad choices (enhanced patient–surrogate agreement on decisions) • confidence felt by surrogate decision-maker in making decisions • less anxiety, depression, and post-traumatic stress experienced by family in bereavement. There is insufficient evidence that ACP can influence the number of admissions and whether patient choices are ultimately followed in end-of-life care.
Preparedness of nephrologists to commence ACP	360 (1)	Low	Nephrologists were more prepared to embark on ACP if they were aware of the guidelines of the Renal Physicians Association on shared decision-making.
Comfort of nephrologists in end of life conversations	26 (1)	Low	Nephrologists were more comfortable in end-of-life conversations if they had completed workshops on communication skills.

associated with better preparedness to perform ACP [5]. Workshops on communication skills can also enhance physicians' comfort in discussing end-of-life issues [60].

Need for Further Research

We need scalable ACP interventions to enhance advance care plan completion. Targeting all stakeholders, including physicians, patients, and caregivers, may result in better chances of success with an ACP intervention. Future research is needed to study how often patients' ADs are followed near their end of life. In addition, we need research to explore what challenges nephrologists face in their communication with patients. Potentially, this may allow them to benefit from evidence-based identification of the factors associated with effective ACP conversations.

The Challenges for Nephrology in ACP

Currently, we are at an apparent impasse in conducting ACP with patients with ESKD:

- Professional bodies within nephrology have issued clear recommendations for completion of advance care plans with patients with CKD, yet uptake of ACP remains limited.
- Multiple observational studies show that many patients wish to communicate with their nephrologist about their future medical care in the event they lose capacity.
- There are known barriers to the initiation and completion of advance care plans, including absence of professional training and personal discomfort.
- There are few intervention and effectiveness studies.

The pathway through this impasse is indeed challenging. Resolution will involve a combination of three vital developments: (i) the undertaking of large, robust intervention and effect studies, (ii) an attitudinal shift by nephrologists toward a greater openness and confidence in conducting all challenging conversations, including development of ACP, and (iii) formal training of nephrologists and fellows in communication skills, including in conducting ACP. ACP should be understood in the broad context of effective and open communication with patients who have CKD regarding treatment options such as dialysis or CKM, informed consent, advance care plans, dialysis withdrawal, and end-of-life care. Education can foster this openness through formal communication training and role modeling of good communication skills by nephrologists to their trainees.

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Conclusion

ACP is an essential component of care of patients with CKD. Nephrologists need to engage patients in ACP conversations and acquire the necessary communication skills to conduct such conversations. For any patient, a diagnosis of advanced CKD and/or any change in social or health conditions should serve as a trigger to initiate ACP. However, only a few randomized controlled trials have tested ACP interventions. We recommend that nephrology fellowship curricula and board certification examinations should emphasize communication skills to help nephrologists undertake a major change in ACP practice.

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Conservative Kidney Management and Dialysis Withdrawal

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Introduction

The advent of dialysis transformed end-stage kidney disease (ESKD) from a universally fatal diagnosis to a chronic illness. However, the physical and psychological burdens of maintenance dialysis (e.g. for fatigue, dizziness, dialysis access-related procedures, and travel to and from dialysis) are highly prevalent, are often severe and undertreated, and correlate directly with impaired quality of life (QOL) [1–5].

These issues are disproportionately higher for older patients with ESKD or those with multimorbidity. This is a troubling reality as rates of dialysis initiation among older patients have increased by more than 50% in the United States alone and dialysis may not increase life expectancy for patients over the age of 75 years with significant comorbid conditions, particularly ischemic heart disease and dementia [6–8]. Moreover, initiation of dialysis often means that patients are committing themselves to continued intensive patterns of healthcare utilization and much of their time will be spent going to and from dialysis or in the hospital or nursing facilities [9–11].

Therefore, for a subset of the ESKD population the harms of dialysis may outweigh its benefits or prolong a state of suffering. For this subset, foregoing or stopping dialysis may be appropriate. The purpose of this chapter is to review the definition, epidemiology, content, indications, and decision-making regarding conservative kidney management (CKM) and dialysis withdrawal as treatment options for patients with ESKD.

Definitions

Defining CKM

CKM is a treatment option for patients with ESKD that, through shared decision-making and holistic patient-centered care, emphasizes QOL, active symptom management, and advance care planning but does not include dialysis (Table 55.1) [12]. The guiding principle in CKM is to align all care with the patient's preferences to achieve his or her personal goals, which typically focus on improving symptoms and enhancing QOL. While interventions to delay progression of kidney disease and manage the complications of chronic kidney disease (CKD) may still play an important role in CKM, they drive care only if they also help the patient achieve their specific goals. CKM requires highly integrated communication and care plans with tailor-made processes and interventions to address unique patient needs and unique family/community circumstances. Careful planning is necessary to link and transition patients at various points along the continuum of care such as between primary, secondary, and tertiary care, between community-based and institutional care, and between acute care and long-term care. It may require involvement of mental healthcare, social services, and specialist palliative care and hospice services. Multidisciplinary care teams are required to deliver optimal CKM. Many of these patients will live for several years following the decision for CKM so their care will require the full spectrum of kidney supportive care services, not just terminal, end-of-life care.

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Table 55.1 The core components of CKM.

CKM is planned, holistic patient-centered care for patients with ESKD that includes: • shared decision-making • active symptom management • advance care planning • psychosocial and family support • cultural and spiritual domains of care • interventions to delay progression of kidney disease • interventions to minimize the risk of adverse events or complications CKM does not include dialysis.

Source: Davison et al. [12].

Defining Dialysis Withdrawal

It may appear that dialysis withdrawal is simply the stopping of dialysis prior to death. However, dialysis withdrawal has been defined variably in studies examining mortality preceded by withdrawal and none have yet been validated [13]. For example, some have defined dialysis withdrawal based on time without dialysis, such as dialysis stopped longer than 3 days (the usual interdialysis interval) before death while others have defined dialysis withdrawal as death only if signs of uremia were present because dialysis was stopped prior to death [14, 15]. Here, we consider dialysis withdrawal as the conscious decision to discontinue dialysis because its overall burden was considered too high or it was resulting in the prolongation of life with an unacceptably poor quality.

Epidemiology

The Epidemiology of CKM

Establishing the incidence and prevalence of CKM is difficult, in part because patients who do not receive dialysis are not necessarily receiving *comprehensive* CKM, which as described here includes a full range of services. Others may not initiate dialysis because their ESKD has not been diagnosed or they are receiving *choice-restricted conservative care* due to limited access to kidney replacement therapy [12]. None of these scenarios are consistent with the above definition of CKM.

The evidence on the incidence or prevalence of CKM based on national data is limited to Australia and Canada. A population-based study in Australia from 2003 to 2007 found that among patients with incident ESKD for every one that received dialysis or a transplant there was one who did not [16]. A community-based cohort study in Canada found the same [17]. However, CKM in these cohorts was defined by the presence or absence of dialysis and may not actually represent an active choice for CKM. In the United States, the national registry begins collecting information on ESKD patients at the initiation of dialysis so national estimates for CKM are unknown. One study using administrative data and in-depth chart reviews of a national cohort of patients receiving care within the Department of Veteran Affairs (the largest integrated healthcare system in the United States) between 2000 and 2009 found that only about 3% of patients (mean age 75 years) had made a decision to not pursue dialysis [18].

The Epidemiology of Dialysis Withdrawal

Estimates of how often patients opt for dialysis withdrawal are also not well understood, in part due to variable definitions of what constitutes withdrawal as noted earlier. We do know, however, that withdrawal of dialysis has increased as an official cause of death for patients with dialysis-dependent ESKD [19–21] though variation persists with regard to the rates reported worldwide [22]. Withdrawal rates in the United States and Canada may be higher than those of European counties with 8–31% and 2–7%, respectively [19, 21, 23–25].

Patient-level factors associated with higher likelihood of withdrawal include white race, female gender, and increased age, though not all studies have found a gender association [26] and one study noted an association with cerebrovascular disease [27]. Increasing rates of medical events and hospitalization in patients immediately prior to withdrawal [26] suggest that declining health and accelerated clinical morbidity are motivating factors for withdrawal. A number of system-level barriers, including financial incentives for continuing dialysis, eligibility issues with hospice, lack of outpatient systems for providing palliative care, and a lack of communication and prognostication skills of the nephrologist, have been cited as important factors driving lower rates of withdrawal [28]. These factors will be explored further in the context of decision-making discussed below.

Decision-making around CKM and Dialysis Withdrawal

It is important to emphasize that decisions for CKM, dialysis, and dialysis withdrawal should be proactive, deliberate, and directed by patient preferences and values. It must also be emphasized that neither CKM nor dialysis withdrawal mandates a cessation of care [29, 30]. Explaining treatment options to patients includes the assurance that they will

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receive care to optimize QOL, including active symptom management and assistance with care coordination and communication with all involved healthcare providers. This will help reassure patients that receiving the treatment and care that matters most to them is of primary importance, regardless of the care pathway they choose.

Unique Aspects of Informed Consent in Patients with CKD

Informed consent and the practice of advance care planning (discussed further in Chapter 54) empowers patients, families, and physicians by aligning decisions about future treatment with patient values, wishes, and evolving clinical circumstances. Reports that patients regret having started dialysis [1], along with the high prevalence of both cognitive impairment [31] and depression [32] in patients with CKD, underscore the importance of assuring that a patient's consent is based on an informed decision. Furthermore, concerns that patients with ESKD receive life-sustaining therapies more often than patients with other terminal illnesses [2] and that many initiate dialysis by default rather than by deliberate decision point to the need for proactive discussion and a dialogue that explores patients' goals, values, and preferences for care, including end-of-life care.

The initiation of dialysis presumes that a process of communication between the patient and physician has taken place, that sufficient information has been provided that describes all the potential harms and benefits of each available treatment option, and that consent to undergo the dialysis procedure has been given. Provision of informed consent for dialysis therefore involves much more than the completion of a legal document that authorizes kidney replacement therapy or the presence of basic documentation stating that the patient accepts the risks associated with the actual dialysis procedure such as low blood pressure and pain with access cannulation. In a healthcare culture where the distinction between the opportunity to extend life and the obligation to do so is often blurred, the informed consent conversation commands attention to a number of pertinent and unique considerations (Table 55.2).

The ethical and legal elements of a valid informed consent to initiate dialysis include the requirements that a patient have decision-making capacity, that consent be voluntary, that information is provided in an understandable manner, and that the risks be presented and alternative options explored [33]. Although application to practice may differ by country, the essence of these requirements transcends geography and international differences in the provision of care.

Table 55.2 Unique aspects of informed consent for patients contemplating CKM or dialysis.

- Patients with significant comorbid illness may not live long enough to progress to the need for dialysis.
- CKM may confer a survival benefit similar to or greater than dialysis for a select group of patients.
- CKM may be preferable to dialysis in some patients for whom the anticipated burdens of dialysis are expected to detract from QOL.
- Functional and cognitive decline may occur rapidly in many older patients starting dialysis, which will impact the overall experience of dialysis.
- Patients' preferences and wishes may change as their clinical or social context evolves.

Preferences and a decision to pursue, continue or withdraw from dialysis may be dynamic, requiring ongoing discussion and the acceptance that emotional, cultural, and social contextual factors will impact the decision-making process [29, 30]. Emotions such as fear or denial may impact a patient's ability to engage in a discussion of what they might perceive is a choice between life and self-imposed death. Specific issues to address include the impact of dialysis on daily life, anticipated clinical course and prognosis, potential for changes in functional status, and alternative treatment choices such as choosing to forego dialysis altogether [12, 34, 35]. The clinical implications of this is that physicians have ethical and legal obligations to present an individualized, patient-centered approach that for some patients includes the likelihood that dialysis may increase suffering while not prolonging life [35–37].

Shared decision-making, recognized as the "pinnacle" of patient-centered care and the accepted model for medical decision-making, is a key component of informed consent and particularly relevant to patients with ESKD contemplating the initiation of renal replacement therapy (further discussed in Chapter 81) [38]. Even for older patients or those with substantial comorbidity, some may be willing to accept a high symptom burden with dialysis as well as its attendant complications based on the hope that it will extend their lives while personal preferences and values may direct others toward a conservative care pathway that does not include dialysis [39–41]. Changes in patient status must be anticipated to ensure that the informed consent process is dynamic and that contextual issues are monitored and considered as life and clinical circumstances evolve. Independent of unique circumstances, patients' preferences may also change over time [42]. Given all these factors, providing informed consent to patients with advanced CKD is complex and can be extremely challenging [43]. Patients' consent or

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refusal for dialysis commands attention and respect, and nephrologists are well poised to take responsibility for ensuring the integrity of this process.

For Whom is CKM Most Appropriate?

The evidence around the benefits and outcomes with CKM is limited and has been well summarized in two systematic reviews [44, 45] with a more recent large Canadian study [46]. These data are observational with numerous limitations making it difficult to pool data and assess the impact of dialysis vs. CKM. These limitations have been well described [47] and include small numbers of patients receiving CKM, mostly limited to those managed by nephrologists, wide variation in the estimated glomerular filtration rate (eGFR) cutoff inclusion criteria with lead-time bias, and significant differences between patients receiving dialysis vs. CKM resulting in mortality biases. By random effects meta-analysis, patients choosing CKM are older (80.0 years vs. 71.5 years) and are less likely to be able to care independently for themselves with lower Karnofsky scores (62.8 vs. 73.0) compared to patients choosing dialysis [45]. They are also more likely to have diabetes and be women than those choosing dialysis. It is unclear how decisions for dialysis or no dialysis are made in these studies. As a result patients receiving what is termed CKM are a heterogeneous population, including at least three groups of patients whose survival will be very different. These groups include (i) patients suitable for dialysis who choose not to receive it, (ii) older people with multimorbidity who are not offered dialysis, and (iii) patients who lack capacity and may not be offered dialysis [47]. There is also a lack of standardization or clarity in reporting of the care provided for patients who are labeled as receiving CKM.

Keeping in mind these limitations, the evidence to date demonstrates a survival advantage with dialysis for most patients compared to CKM. A retrospective Canadian cohort study used linked administrative and laboratory data to identify adults ≥65 years in Alberta with two outpatient eGFR < 10 ml/min/1.73 m^2, spanning ≥90 days (2002–2012). Overall, 838 patients were identified with a mean age of 79 years, 48.6% male, and mean eGFR of 7.8 ml/min/1.73 m^2. Receiving dialysis vs. no dialysis was associated with a significantly lower risk of death for the first 3 years of follow-up (hazard ratio [HR] 0.59), but not thereafter (HR 1.22) [46]. Dialysis, however, was associated with a significantly higher risk of hospitalization (HR 1.40). This population study included all three groups of CKM patients identified above, cared for by non-nephrologists as well as nephrologists. For patients not on dialysis, the care they received is unknown and may not include the core components of CKM as previously defined.

In the nine studies that examined patients cared for by nephrologists and which performed multivariable Cox proportional hazards regression models, five showed a survival advantage for dialysis vs. CKM, although four of these five studies concluded that the survival advantage with dialysis was reduced substantially by older age and the presence of comorbidities [45]. In a meta-analysis limited to the three cohorts that included patients ≥65 years and eGFR < 15ml/min/1.73 m^2, patients choosing dialysis had a pooled adjusted hazards ratio for mortality of 0.53 ($P = 0.02$) relative to CKM, after accounting for both age and comorbidities. The survival benefit with dialysis was no longer significant when restricted to patients ≥75 years. Frail patients often experience accelerated functional and cognitive decline after starting dialysis [48, 49] and those residing in long-term care facilities at the time of starting dialysis have especially poor outcomes [49].

To summarize, while age alone is a poor predictor of survival, patients older than 75 or 80 years with functional and cognitive impairment and multimorbidity, especially heart disease, are at an increased risk for poor outcomes on dialysis with limited if any survival advantage. These are the people most likely to benefit from CKM. Patients who receive CKM spend less time in hospital [45] and are more likely to access timely palliative care services [50].

Decision Aids to Facilitate Educating Patients and Families about the Option for CKM

Although decisions to forego or stop dialysis are often difficult, few patient decision aids (PDAs) present CKM with any depth. The most comprehensive PDA currently available is the freely accessible CKM PDA from the collaborative effort of the Kidney Supportive Care Research Group (University of Alberta) and Alberta Health Services in Canada [51]. Based on state-of-the-art implementation science and patient-orientated research with high stakeholder engagement, this tool provides patients, families, and care providers with information on CKM and dialysis. It is a highly interactive, online resource that incorporates patients' values, preferences, and overall goals of care with patient-specific prognostic markers of age, functional status, comorbid conditions, cognitive function, and living circumstances to compare dialysis versus CKM [51, 52]. A similar but paper-based tool was developed by the Ottawa Hospital CKD team in Ontario, Canada. The Ottawa PDA also provides patient-specific risks and benefits in the context of the patient's personal values and is designed to be used one-on-one with a decision coach trained in decision support.

An upcoming PDA for the decision between CKM and dialysis is the OPTIONS tool from Australia. This tool will be an illustrated workbook with detailed help on making

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care decisions around CKM, although it is unclear if it includes an individualized prognostic component similar to the above two PDAs [52].

For any PDA to be effective, clinicians must introduce the PDA to patients and families as well as have the communication skills and knowledge to facilitate decision-making. Translations into non-English languages are needed for all.

When to Consider Dialysis Withdrawal

As dialysis transforms from a therapy that is life-enhancing to one that is life-prolonging, patients as well as loved ones may see decreasing value in continuing to dialyse. Symptoms that worsen or are not alleviated as hoped may prompt some patients to request discontinuation of dialysis, believing that the burdens of dialysis are no longer worth the benefits they receive [53]. Others experience such poor QOL that they feel little or no hope for an experience that is better than status quo. Severe, unrelenting depression or loss of the will to live may constitute sufficient rationale for certain patients to withdraw [12, 34]. Withdrawal from dialysis is an appropriate treatment option for any patient in whom the burden of treatment becomes irreversibly greater than their perceived benefits.

Unfortunately patients may not discuss end-of-life issues, including wishes to withdraw from dialysis with their families. Patients may also not state independently or explicitly the extent of their suffering or their desire to consider dialysis withdrawal to their care team. Instead, they often look to their healthcare providers for guidance [1, 54], with the expectation that their provider will raise these issues when they become relevant for each individual [55]. This raises the importance of ensuring all patients and their caregivers are aware of the treatment option to withdraw if the burden of dialysis care becomes irreversibly greater than the benefits as perceived by the patient. Despite evolving knowledge of the trajectory of illness in ESKD, identifying this particular point in time can be difficult when clinical decline is subtle [56, 57]. However, when recognized and acknowledged, it may serve as an indication for considering withdrawal (Figure 55.1). Clinicians must also be vigilant for clinical cues in their communications with patients such as expressions of unrelenting suffering.

Consideration of dialysis withdrawal is also appropriate for patients who no longer have decision-making capacity and whose properly appointed agent requests dialysis discontinuation based on the patient's best interests, patients with irreversible, profound neurological impairment who lack signs of thought, sensation, purposeful behavior or awareness of self or environment, patients whose condition no longer renders them able to cooperate with the technical process of dialysis, and patients with terminal illness from nonrenal causes (where no benefit from continued dialysis is anticipated) (Table 55.3) [12, 34].

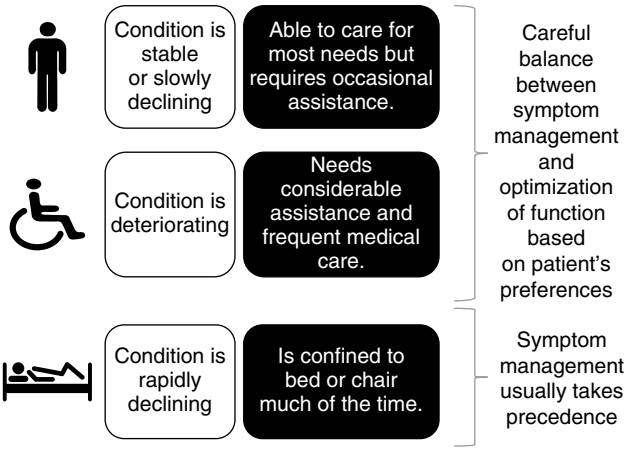

Figure 55.1 CKM should take into consideration the patient's general condition and prognosis.

Educating Patients and Families about the Option of Dialysis Withdrawal

Unfortunately no PDAs currently exist to facilitate conversations and decision-making around dialysis withdrawal. Barriers to this process include patient, family, and physician factors. If not informed, patients may be unaware of the option to withdraw or feel that their decision will be deemed unacceptable and/or unsupported by the medical team. Others may consider withdrawal spiritually unacceptable, "a sin" or an act of suicide. Others may believe that withdrawal constitutes "giving up" and/or fear that their loved ones will not accept their decision. Patients may be fearful of the dying process following withdrawal and uncertain of the care they will receive.

Table 55.3 When to consider discussing dialysis withdrawal.

- Patients in whom the burden of treatment becomes irreversibly greater than its perceived benefit
- Patients who no longer have decision-making capacity and who appear to no longer be benefitting from dialysis
- Patients with irreversible, profound neurological impairment who lack signs of thought, sensation, purposeful behavior, or awareness of self or environment
- Patients whose condition renders them unable to cooperate with dialysis
- Patients with terminal illness from nonrenal causes without anticipated benefit from continued dialysis

Sources: Davison et al. [12] and Renal Physicians Association [34].

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These issues must be explicitly addressed, including reassurance that patients will be cared for and not abandoned. Patients and families may also differ in their motivation to stop dialysis, a scenario that further complicates the decision-making process and underscores the importance of discussing the option for dialysis withdrawal in early advance care planning conversations that include family and surrogate caregivers [30, 57].

Physicians and other healthcare providers may be reticent about instituting discussions because of uncertainty in estimating patient-specific prognosis, a lack of understanding of patients' wishes, and/or the perception that these conversations will be overly distressing to patients and destroy hope. However, patients tend to understand and accept the inherent uncertainty in predicting individualized outcomes. Moreover, proactive discussions about options for end-of-life care have been reported to reinforce trust and promote hope [58] while impacting patient choice [59, 60]. Lack of training and inexperience on the part of healthcare providers has been cited as a barrier to this conversation and some physicians may harbor an ethical opposition to dialysis withdrawal or be unwilling to communicate this option for other personal reasons [61–63].

Setting the stage for patients experiencing clinical decline requires an honest evaluation and assessment of an individual patient's current clinical status, their prognosis and potential for further decline and an acknowledgement that ongoing dialysis may further reduce the benefit–burden balance. In situations where a patient lacks decision-making capacity, the patient's designated surrogate decision-maker must understand clearly the patient's clinical situation. Without this support, patients and families may struggle with what they perceive as choosing death rather than allowing death to occur [64].

It is important to discuss the option of withdrawal at the outset of renal replacement therapy discussions in all patients, but it is particularly pertinent in those who initiate dialysis despite a poor prognosis. Key points of education for patients and families considering withdrawal of dialysis are outlined in Table 55.4. First and foremost, this includes the promise that withdrawing from dialysis will not result in abandonment and does not mean "no care." Clinicians must acknowledge the role of patients' fears and emotions, social factors, depression, and/or high symptom burden in the decision-making process and address potentially remedial factors contributing to the decision. The specifics of the dying process after withdrawal, especially with regards to potential symptoms patients may experience, how these can be treated, and a time frame, are key components of the conversation. Patients should be made aware that palliative care is available irrespective of a decision to withdraw from dialysis. Serial conversations and incremental introduction of available palliative interventions may be needed in patients who are conflicted or where reversible factors contributing to suffering are driving patient choice. Wishes for and the availability of hospice care to relieve suffering and provide support can also be discussed and may be factored into the decision. While hospice may be an appropriate consideration following withdrawal of dialysis, it may also be available for patients who remain on dialysis with an extremely limited expectation for survival.

Table 55.4 Key education points for patients and families contemplating whether to pursue, forego, or withdraw from dialysis.

- Conservative kidney management without dialysis is every patient's option and choice.
- Choosing to forego or withdraw from dialysis does not mean "no care."
- Palliative and supportive care is available irrespective of whether dialysis is chosen, continued or withdrawn.
- Hospice is an appropriate consideration for patients following withdrawal of dialysis or for patients who have chosen CKM in the terminal phase of their illness.
- Estimates of survival individualized to the patient are important to patients and families. For patients withdrawing from dialysis this should be given in days.
- Anticipatory plans for dealing with distressing symptoms are important for patients choosing CKM or deciding to withdraw from dialysis to avoid unnecessary suffering.
- Preparing for acute symptom management may pre-empt the need for heat of the moment decisions in patients contemplating their options and prevent the unnecessary use of acute care resources.

When CKM is the Chosen Treatment Option

The Illness Trajectory from the Decision for CKM through to Death

Prognostication for patients with CKD is challenging given the great variation in individual illness trajectories and accurate prognostic models are limited. This is particularly true for patients with ESKD receiving CKM. Patients are anticipated to pass through several stages, as outlined in Figure 55.1. The patient's eGFR does not necessarily predict their overall clinical picture or their survival. Patients with an eGFR of 6–15 ml/min/1.73 m^2 may experience minimal symptom burden and remain functional and stable for years, although some may have high symptom burden and/or deteriorate rapidly over a few months [44, 50]. Patients with an eGFR of ≤5 ml/min/1.73 m^2 typically have a life expectancy measured in weeks to a few months. Understanding the overall health

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status of the patient is a better predictor of outcome and provides a more reliable guide to determining appropriate care. For patients who remain relatively stable and functional, maximizing their QOL requires a careful balance between promoting function and addressing symptom burden. For patients who spend much of their time confined to bed or have a life expectancy limited to weeks, comfort and control of symptoms generally takes precedence.

Standards for Clinical Care for Patients Receiving CKM: CKD Complications

There are minimal studies that address specifically how to optimize CKM. As a result there is great variation in how this care is both conceptualized and delivered. Most clinical guidelines for patients with advanced CKD focus on slowing the progression of CKD and minimizing morbidity and mortality. This is done through strategies such as optimizing blood pressure control, normalizing biochemical parameters, and primary prevention through the use of certain medications such as statins and angiotensin converting enzyme inhibitors or angiotensin receptor blockers. However, this is not the focus of care for most patients who have chosen CKM. Rather the aim is to optimize clinical outcomes such QOL and physical and cognitive function. To accomplish this in patients who tend to be frail, CKD clinical standards and expectations need to be adjusted. Despite a lack of robust evidence specific to CKM, recommendations were developed that integrate the existing evidence and expert opinion from nephrology, geriatric medicine, and palliative care. These recommendations are part of an integrated CKM clinical pathway that is freely accessible (www.ckmcare.com) and they have been recently published [65]. The key elements of these recommendations are outlined in Table 55.5. They reflect the priorities of comfort, QOL, and safety, ensuring that all treatment decisions align with patient's values and preferences, and are intended as a starting point toward reaching consensus and generating further evidence for optimal CKM.

Table 55.5 Recommendations for managing the progression and metabolic complications of CKD for patients receiving CKM.

Rationale for recommendations	Recommended interventions
Blood pressure (Musini VM, Muller M, Benetos A)	
The primary goal of blood pressure control in CKM is to optimize QOL by preserving physical and cognitive function, minimizing the risk of falls from hypotension or orthostatic hypotension, while avoiding very high readings that might precipitate an acute cardiovascular event. Decisions about specific medications will depend on the patient's comorbidities.	Blood pressure targets can be relaxed for *most* CKM patients to <160/90 mmHg. This applies to patients with diabetes as well. The geriatric literature suggests a target systolic blood pressure of 160–190 mmHg is reasonable for frail patients near the end of life [66]. Based on expert opinion, the lower end of this target has been identified as being appropriate for CKM.
Dyslipidemia (Benetos A, Kutner JS, Silveira MJ)	
There is no evidence that statins provide benefit in the context of significant frailty or in the last year or two of life. Statin therapy takes years to accrue benefits. Advanced age and multimorbidity are risk factors for adverse effects of statins, including myopathy and a potential link to cognitive deficits. A randomized trial of discontinuing statin therapy in patients with life-limiting illness suggested that cessation was not only safe, but it improved QOL.	Care providers, in discussion with the patient, can discontinue statins.
Sodium restriction	
Sodium intake may be associated with volume overload leading to breathlessness and symptomatic peripheral edema. Sodium restriction, however, influences palatability. Strategies should balance symptom management and the patient's enjoyment of food and nutritional status.	Diuretics and dietary sodium restriction is recommended to assist with volume control if volume overload is contributing to symptoms such as breathlessness or symptomatic peripheral edema.
Anemia (Rogers SD)	
Anemia can contribute to fatigue and breathlessness. The purpose of treating anemia would be to reduce these symptoms as opposed to reducing cardiac mortality or morbidity.	Interventions include the use of erythropoiesis stimulating agents and iron supplements. Anemia-related blood work every 3 months is appropriate but should be based on patient preference and symptoms. When a patient starts spending most of their time confined to bed or chair and/or is near the end of life, it is no longer appropriate to manage fatigue and breathlessness by addressing anemia and anemia treatment can be stopped.

(*Continued*)

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Table 55.5 (Continued)

Rationale for recommendations	Recommended interventions
Acidosis (Kopple JD [79], Raphael KL [80])	
Metabolic acidosis can contribute to fatigue, bone loss, muscle wasting, and malnutrition. Treatment is aimed at improving these symptoms.	Oral sodium bicarbonate. It is reasonable to monitor CO_2 every 3 months if the patient is being treated or is symptomatic. If the patient finds the pill burden too great, or when the patient can no longer swallow, treatment should be stopped.
Calcium and phosphorus balance (Rayner HC 2017, Shinaberger CS, 2008)	
Current CKD guidelines aim to normalize serum calcium, phosphate, and parathyroid hormone levels to prevent bone abnormalities and vascular calcification. However, it is not clear that there are benefits to normalizing these factors in CKM patients in the last years of life. Rather, there is the possibility of harm in promoting lower protein intake in patients already at high risk for protein malnutrition [67]. The focus is on promoting and maintaining adequate nutrition, avoiding malnutrition and inflammation, and liberalizing the diet. Changes in the metabolism of calcium and phosphorus may contribute to (i) myalgias, arthralgias, and pseudogout, and (ii) restless legs syndrome. Interventions would only be promoted for possible benefit of these symptoms.	The recommendation is to focus on adequate nutrition rather than normalizing biochemistry. If elevated phosphorus levels were felt to be contributing to pain or RLS, interventions would include a phosphorus-restricted diet and the use of phosphate binders, monitoring for the impact on overall QOL, symptom burden, and nutritional status. It is reasonable to check calcium and phosphorus levels every 3 months if patients are being treated or are symptomatic. Parathyroid hormone levels do not impact decision-making for patients being cared for with CKM, therefore there is no need to monitor.
Vitamin D	
Vitamin D deficiency may play a role in the symptoms of fatigue, weakness, and muscle loss. Supplementation should only be considered if deficiency was felt to be contributing to these symptoms.	Low-dose active vitamin D (vitamin D analogue) replacement. There is no additional benefit in monitoring parathyroid hormone levels.
Hyperkalemia	
Hyperkalemia predisposes patients to cardiac arrhythmias and sudden death. Acute treatment of hyperkalemia is appropriate if consistent with the patient's goals. If the patient wishes to liberalize their potassium intake, the risks of lifting the restriction must be explained clearly.	Interventions include a potassium-restricted diet and potassium-binding resins such as patiromer. Consider sodium polystyrene sulfonate for life-threatening hyperkalemia. For those aiming to maintain normal potassium levels, it is reasonable to monitor potassium levels monthly.

Source: Adapted with permission from Davison SN on behalf of the Kidney Supportive Care Research Group, University of Alberta and Alberta Health Services. Conservative Kidney Management: Patient Decision Aid. Alberta, Canada, 2016. CKM Pathway at http://www.CKMcom.care.

Symptom Assessment and Management for Patients Receiving CKM

Only a few studies have looked at symptoms in patients receiving CKM but the symptom burden appears to be high and similar to that of patients who intend to dialyze or are receiving dialysis (this is discussed further in Chapter 52) [44]. There are even fewer studies that look specifically at the impact of a CKM program on the symptom burden of patients. An Australian kidney clinic that integrates palliative care for patients receiving CKM found that although patients who chose CKM had a worse symptom burden and physical composite SF-36 QOL scores than others at their initial clinic visit, the majority maintained or improved symptom control and QOL at 12 months [68]. In 122 CKM patients, 57% had stable or improved symptoms and 58% had stable or improved QOL. This cohort of CKM patients had a median survival of 16 months with 68 (56%) patients dying over the study period. This was in comparison to the patients who intended to dialyze, of whom only 41% had stable or improved symptoms and only 55% had stable or improved QOL.

Patients underreport symptoms unless they are assessed explicitly [69, 70]. It is therefore critical to assess patients at each clinic visit for physical and emotional symptoms using a validated tool like the Edmonton Symptom Assessment System Revised: Renal (ESAS-r: R) or the Integrated Palliative Care Outcome Scale-Renal (IPOS-Renal) (see Chapter 52 for further discussion on available tools for symptom assessment).

The aim of treatment is to ameliorate symptoms that are adversely impacting the patient's QOL as it is not always possible or necessary to resolve them. It is important that clinicians explain this to patients in order to establish realistic expectations. The goal of therapy is to relive the

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overall symptom burden to a level that is tolerable for an individual patient. Care teams also need to take into consideration the overall health and function of their patient. Earlier in the illness trajectory the relief of symptoms may be aimed at promoting social and physical functioning, and the adverse effects of pharmacologic interventions will need to be balanced carefully between symptom relief and optimal cognitive and physical wellbeing. Symptoms may be experienced in complex clusters. It may not be necessary to target all the symptoms at once. For example, restless legs may interfere with sleep and be associated with daytime somnolence, fatigue, depression, anxiety, and an overall poor QOL. When assessing the patient, attempting to understand the root cause for a patient's distress will help guide appropriate management. In the above scenario, targeting the restless legs would be anticipated to improve sleep, energy, and ultimately mood and overall QOL.

The treatments of individual symptoms are outlined in Part 12: Patient-centered care and outcomes (see Chapters 84–89). They are summarized in Table 55.6 with considerations specific for CKM and can be accessed in detail through the integrated CKM pathway [51]. All recommendations follow a similar stepped approach that starts with assessing the patient to rule out contributing reversible factors. The second step is to consider nonpharmacological interventions. Given the frailty and multimorbidity of most CKM patients, these conservative measures are important to explore to promote patient safety before moving on to the third step, which involves pharmacological interventions. Good examples are the management of nausea, vomiting, and pain due to the adverse effects of many of the commonly used agents. For example, ondansetron can be constipating and the dopamine antagonists haloperidol, metoclopramide, and olanzapine cross the blood–brain barrier and can cause extrapyramidal symptoms and exacerbate restless legs syndrome. Opioids for the management of pain and shortness of breath can be extremely constipating and may exacerbate pruritus, restless legs, and terminal agitation.

These CKM recommendations tend to avoid the use of benzodiazepines given the significant risks risk of falls, fractures, and decreased cognition in the frail and older patient. However, they could be considered for patients experiencing significant anxiety. They may also be the only option for restless legs causing distress for patients near the end of life who can no longer swallow.

Table 55.6 Management of symptoms for patients receiving CKM.

Restless legs syndrome (Gopaluni S, 2016; Giannaki CD, 2014)		
Address possible contributing factors	Nonpharmacologic	Pharmacologic
• Anemia and iron deficiency • Hyperphosphatemia • Medications such as dopamine antagonists, antidepressants, and opioids	• Abstinence from stimulants (e.g. alcohol, caffeine, and nicotine) • Mental alerting activities (e.g. puzzles or games) • Optimized sleep hygiene • Exercise	**First line:** Gabapentinoids Gabapentin 50–300 mg nightly or pregabalin 25–75 mg nightly **Second line:** Nonergot-derived dopamine agonists Ropinirole 0.25–2 mg nightly Rotigotine transdermal patch 0.5–3 mg/nightly Pramipexole 0.125–0.5 mg nightly • All these medications should be taken 2 h before sleep
Uremic pruritus (Simonsen E, 2017)		
Address possible contributing factors	Nonpharmacologic	Pharmacologic
• Anemia and iron deficiency • Other: xerosis, drug hypersensitivities, allergies, infestations, contact dermatitis, or inflammation	• Appropriate skincare and moisturizers (e.g. baths with lukewarm water, pat dry, and moisturize with aqueous emollients within 2 min; gentle soaps with no fragrances or additives) • Keep skin cool • Humid environment • Avoid scratching: maintain short, smooth fingernails, encourage gentle massage, wear gloves at night • Very little evidence exists for complimentary therapies but consider phototherapy (UVB) three times weekly for a 3-week trial or acupuncture	**Topical** • Capsaicin 0.025% or 0.03% ointment • Pramoxine 1% • Menthol/camphor/phenol: 0.3% each, either separately or in combination with each other • Gamma-linolenic acid cream 2.2% **Systemic** **First line:** Gabapentin (50–300 mg daily) 1–2 h before sleep. Similarly, pregabalin before sleep (25–75 mg) is also an option. **Second line:** Tricyclic antidepressant such as doxepin 10 mg daily at night

(*Continued*)

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Table 55.6 (Continued)

Nausea and vomiting (Collis E, 2015; Murray-Brown F, 2015)		
Address possible contributing factors	Nonpharmacologic	Pharmacologic
• Metabolic disturbances • Medications, e.g. opioids, antidepressants • Gastrointestinal disturbances, e.g. constipation, delayed gastric emptying	• Manage constipation • Encourage proper oral hygiene • Smaller, more frequent meals; eat slowly • Avoid alcohol • Avoid foods that are greasy, spicy or excessively sweet • Minimize aromas, e.g. cooking odors, perfumes, smoke • Encourage relaxed, upright position after eating to facilitate digestion • Loose-fitting clothing • Consider complementary therapies, e.g. relaxation techniques, acupressure, use of ginger	Recommendations are very specific depending on patient's status but include: **First line:** Ondansetron 4–8 mg every 8 h as needed **Second line:** Metoclopramide 2.5 mg every 4 h as needed. Due to the prokinetic properties, metoclopramide would be first-line treatment for patients with nausea and vomiting due to gastroparesis. **Third line:** Olanzapine 2.5 mg every 8 h as needed OR haloperidol 0.5 mg every 8 h as needed **Fourth line:** For persistent and severe nausea, consider increasing haloperidol to 1.0 mg (maximum 5 mg in 24 h) OR replacing with methotrimeprazine 5 mg orally or 6.25 mg subcutaneously every 8 h as needed. Methotrimeprazine may also be beneficial if there is concomitant anxiety, insomnia, or neuropathic pain.
Breathlessness (Booth S,, 2011; Barnes H, 2016		
Address possible contributing factors	Nonpharmacologic	Pharmacologic
• Anxiety • Anemia • Infection • Pulmonary edema	• Sit in an upright position, e.g. 45° • Position by a window or use a fan to blow air gently across the face • Maintain a humid environment • Pursed lip breathing • Supplemental oxygen • Complementary therapies, e.g. relaxation techniques, music • Consider role of diet: fluids and sodium	• If patient is intravascularly overloaded: furosemide • Low doses of opioids, especially nearer the end of life. Due to its fast action, fentanyl works well in cases where breathlessness is predictable. For shortness of breath that is more constant or unpredictable in nature, consider low-dose hydromorphone, e.g. 0.5 mg PO (0.2 mg subcutaneously) every 4 h around the clock and every hour as needed.
Fatigue and sleep disturbances (Canadian Agency for Drugs and Technologies in Health: 2016; Furey SA, 2014; Yennurajalingam S, 2007)		
Address possible contributing factors	Nonpharmacologic	Pharmacologic
Fatigue • Vitamin D deficiency • Metabolic acidosis • Hypothyroidism, hyperthyroidism, adrenal insufficiency • Anemia • Mood disorder, e.g. anxiety, depression • Medication toxicity, e.g. benzodiazepines, antidepressants, opioids • Sleep disorders Sleep disturbances • Other symptoms as described in this table • Cognitive impairment • Medications • Generalized insomnia • Mood disorders • Apnea	Fatigue and sleep disturbances • Exercise • Nutrition and hydration management • Cognitive and psychological approaches, e.g. relaxation therapy, delegating and setting limits • Energy conservation strategies • Optimized sleep hygiene, e.g. avoid stimulants later in the day, avoid napping, save the bedroom for sleep • Complementary treatments, e.g. acupressure, massage, acupuncture	Sleep Disturbances **First line:** Consider low-dose gabapentin (50–300 mg at night), especially if the patient has concomitant neuropathic pain, restless legs syndrome or uremic pruritus **Second line:** Doxepin 10 mg at bedtime, especially if concomitant pruritus or neuropathic pain **Third line:** Cautiously consider mirtazapine 7.5 mg or zopiclone 3.75–5 mg at night or melatonin 2–5 mg at night

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When Withdrawal from Dialysis is the Chosen Treatment Option

When withdrawal is the chosen course, it is important to provide an explanation of the dying process, the symptoms a patient may anticipate, how these symptoms can be treated, other care requirements and family supports that are required, and an estimated time frame for survival [12, 34]. A suggested process is shown in Figure 55.2. Aligning care to meet patients' needs typically requires detailed attention to symptom management. Dietary restrictions, blood tests or adherence to medications no longer takes precedence. Coordinating care between the multidisciplinary care providers is a key component of providing supportive care. Offering patients the option to change their mind may give them comfort and a feeling of control. This care mirrors the care patients receive in the terminal phase of CKM as described above.

Patients and families should be provided with an estimate of survival following withdrawal from dialysis. Although individual estimates are often difficult to make, reported survival times are 7–14 days on average [24]. The occasional patient may live for over a month or two if there is still residual kidney function.

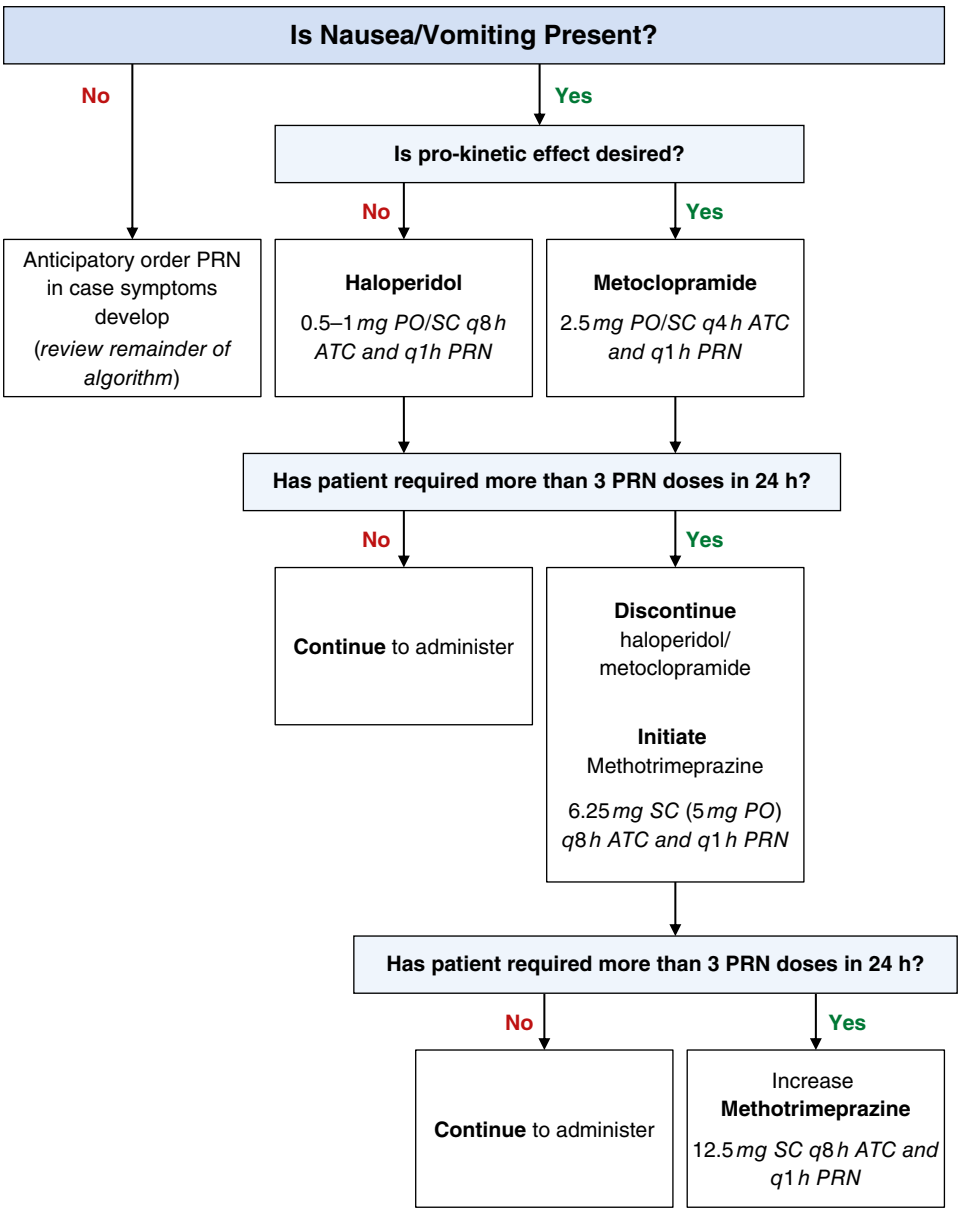

Figure 55.2 Suggested steps for implementing dialysis withdrawal. *Source:* Used with permission from Davison SN on behalf of the Kidney Supportive Care Research Group, University of Alberta and Alberta Health Services. Conservative Kidney Management: Patient Decision Aid. Alberta, Canada, 2016. CKM Pathway at http://www.CKMcom.care.

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Prior to withdrawal, patients should clarify, document, and make available their advance directive, will and durable or medical power of attorney, and, as appropriate, an inventory of bank, brokerage, and financial accounts. Documentation of funeral preferences and/or a written, audio or video message to family and/or friends may be desired [12, 34]. Finally, translating the advance directive into actionable medical orders helps direct care. In some provinces in Canada this is done through Goals of Care Designations and in the United States through Physician Medical Orders for Life-Sustaining Treatment known as POLST, POST, MOLST, or MOST depending upon the state [71]. The patient's preferred location of care and site of death should be determined as death in the preferred location of care is not always feasible. The availability of palliative care services and the potential role of a hospice are important to discuss. Patients' desires for comprehensive symptom control (physical, emotional, and spiritual) and palliative sedation should symptoms become refractory to treatment are key components of these discussions.

Special Considerations for Terminal Symptom Management at the End of Life

For most patients, whether they have chosen CKM or have withdrawn from dialysis, control of symptoms becomes the primary focus in the last weeks or days of life. Management strategies for terminal symptoms are slightly different than chronic symptom management and are summarized in Figures 55.3–55.6.

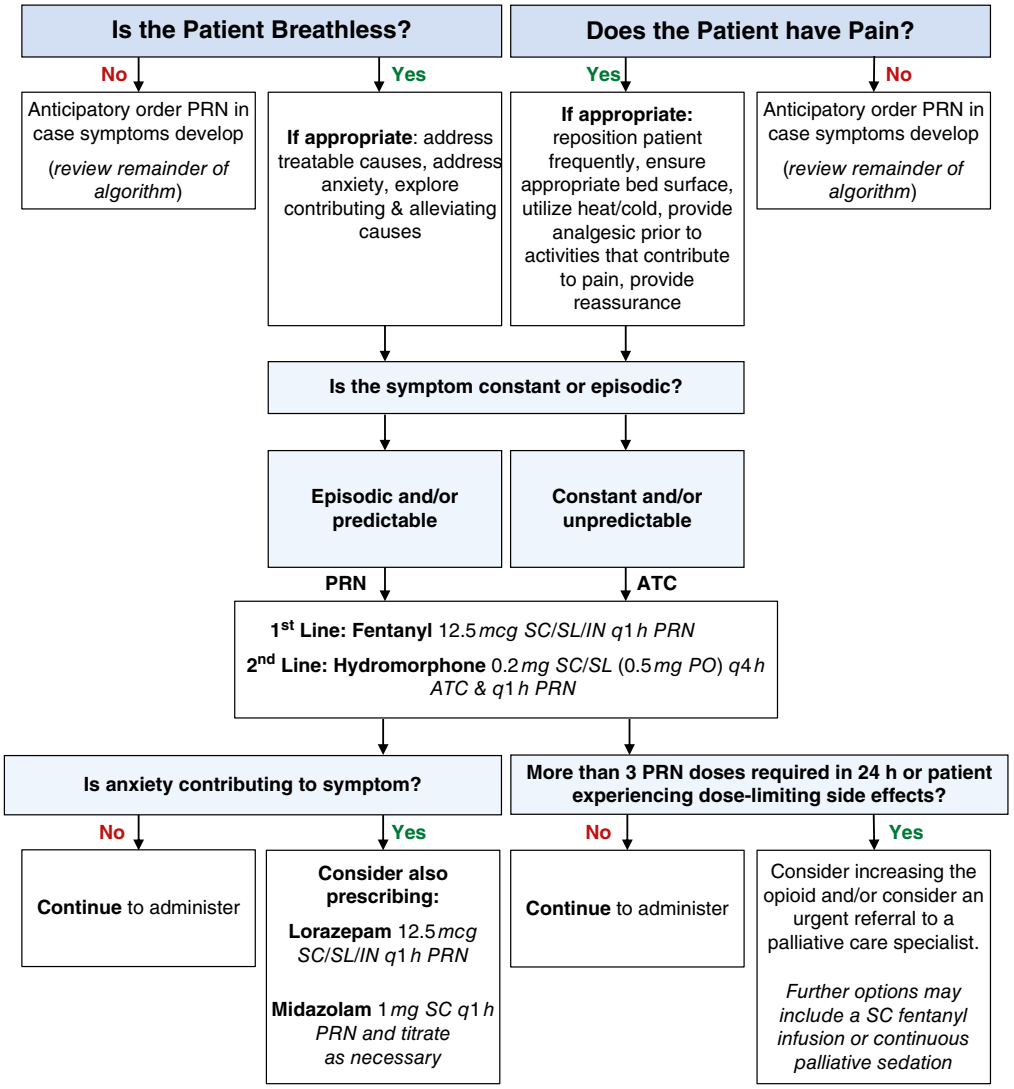

Figure 55.3 Treatment of nausea and vomiting at the end of life. *Source:* Used with permission from Davison SN on behalf of the Kidney Supportive Care Research Group, University of Alberta and Alberta Health Services. Conservative Kidney Management: Patient Decision Aid. Alberta, Canada, 2016. CKM Pathway at http://www.CKMcom.care.

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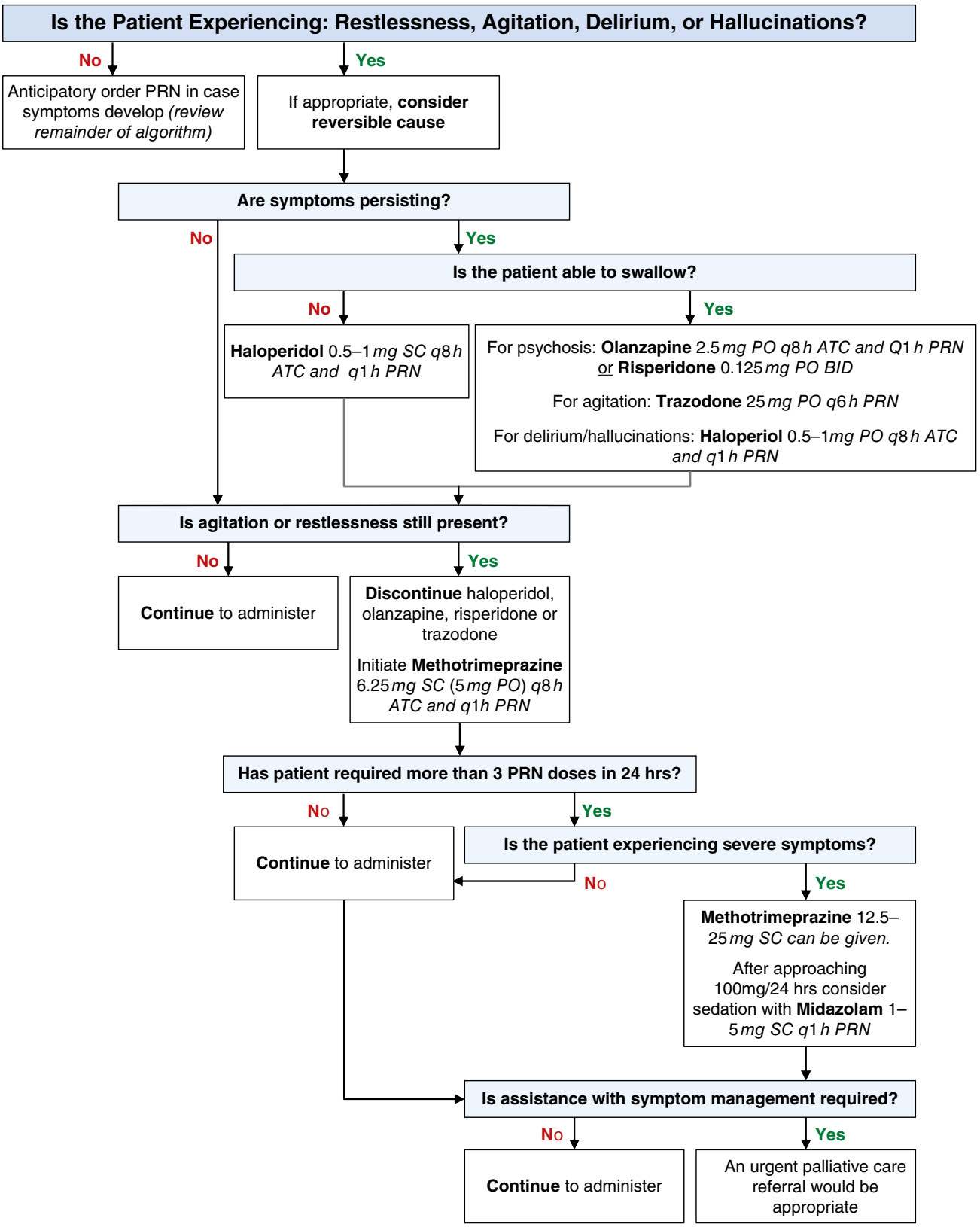

Figure 55.4 Treatment of breathlessness and pain at the end of life. *Source:* Used with permission from Davison SN on behalf of the Kidney Supportive Care Research Group, University of Alberta and Alberta Health Services. Conservative Kidney Management: Patient Decision Aid. Alberta, Canada, 2016. CKM Pathway at http://www.CKMcom.care.

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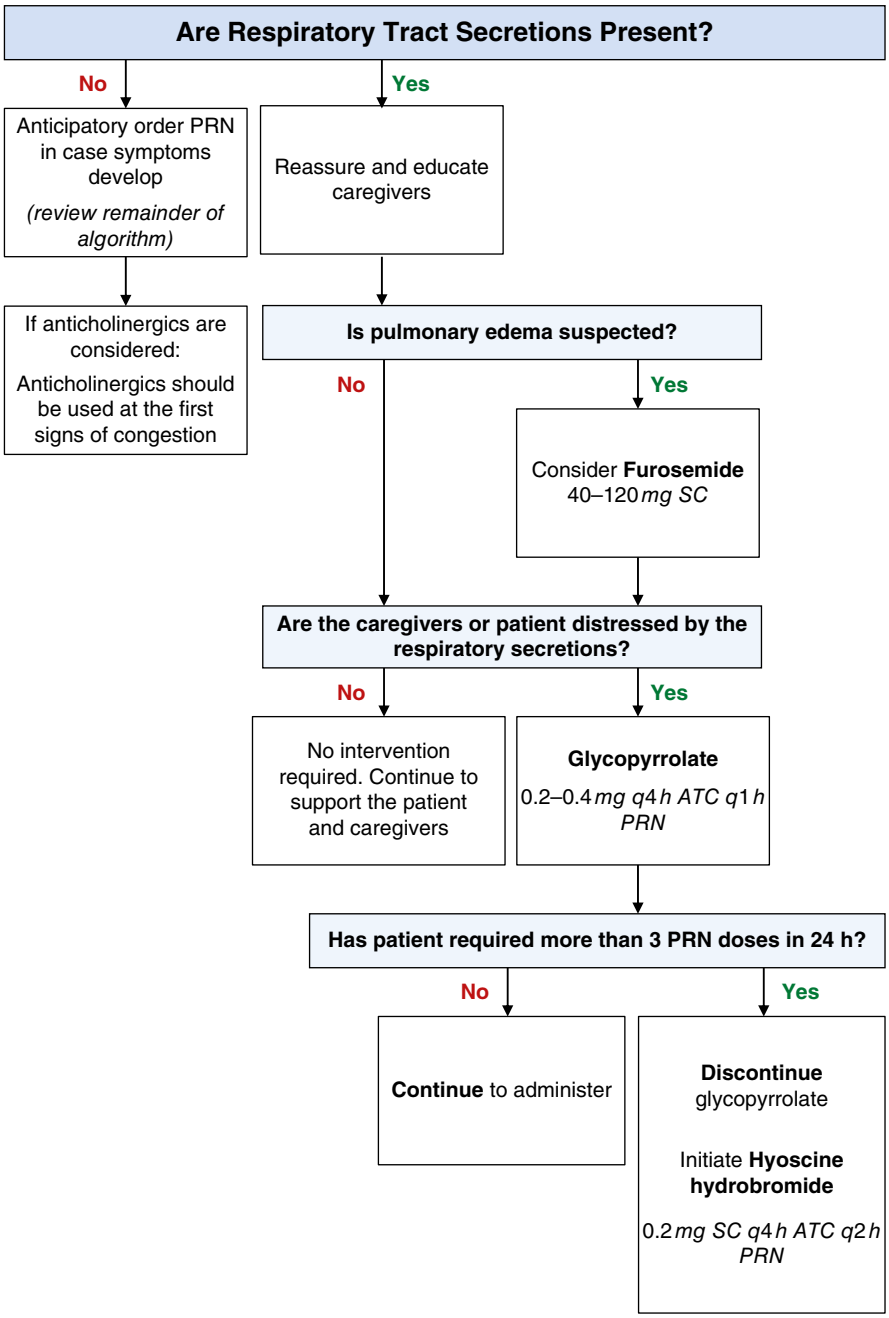

Figure 55.5 Treatment of restlessness, agitation, delirium, and hallucinations at the end of life. *Source:* Used with permission from Davison SN on behalf of the Kidney Supportive Care Research Group, University of Alberta and Alberta Health Services. Conservative Kidney Management: Patient Decision Aid. Alberta, Canada, 2016. CKM Pathway at http://www.CKMcom.care.

Anticipatory prescribing is extremely important to avoid unnecessary suffering. This means that even if patients are not experiencing symptoms, they should still have rapid access to subcutaneous or sublingual medications for pain, shortness of breath, nausea, and agitation so that these symptoms can be addressed rapidly should they occur. For the treatment of nausea and vomiting (Figure 55.3), the dopamine antagonists haloperidol and metoclopramide should not be prescribed together and doses are typically reduced by 50% for patients with ESKD. This is an off-label use for both these medications. Patients should be monitored carefully for extrapyramidal symptoms. For the treatment of pain or shortness of breath at the end of life (Figure 55.4), opioids are the first-line pharmacologic treatment. Fentanyl or buprenorphine is preferred given the pharmacokinetics are minimally altered in ESKD. Hydromorphone is metabolized principally

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to hydromorphone-3-glucuronide, which has no analgesic activity but possibly causes neuro-excitation resulting in agitation, confusion, and hallucinations. In patients receiving CKM or for those who have withdrawn from dialysis, this metabolite will accumulate and might cause toxicity. For this reason, we consider hydromorphone the second-line treatment for ESKD patients in the last days of life if not receiving dialysis. If terminal agitation, restlessness, or hallucinations occur, it is important to rule out medication toxicity (Figure 55.5). In the case of opioid toxicity, it may be necessary to reduce the opioid dose or consider switching to another opioid, i.e. opioid rotation. Terminal respiratory tract secretions can cause sounds colloquially known as a death rattle once a patient is no longer able to clear their saliva and bronchial secretions. This is normal but can be distressing to family members. It is important to educate the family that the patient is usually not disturbed by and is unaware of their noisy breathing. Repositioning the patient may be helpful but suctioning is to be avoided. Medications to reduce secretions can be provided to the patient in an attempt to provide emotional comfort for loved ones (Figure 55.6). Emotional and spiritual support for both the patient and family remain integral to comprehensive end-of-life care. Palliative care consultation and hospice referral may be appropriate for many patients.

Role of Hospice

Patients may benefit from hospice services that address and provide expert symptom management. In addition to clinical monitoring and support, hospice can provide significant social and emotional support to patients and families. Hospice promotes sharing the responsibility of caregiving through scheduled visits and education of loved ones, usually with around the clock availability for questions or concerns that may arise after hours. It is also important to understand that hospice services are not limited solely to patients who have chosen CKM or have withdrawn from dialysis but may be available for patients on dialysis who have an expected survival limited to only a few months.

Despite its broad availability in many countries, hospice care occurs much less frequently among patients with ESKD [56, 72–74] than the general population [75].

Several possible explanations for the underutilization of palliative and hospice care have been proposed and include a lack of knowledge and understanding of palliative care and related services among patients and their families, which may be socially and culturally patterned [76, 77]. Many patients with ESKD have very poor knowledge of palliative and hospice care. Perceptions are often negative, with a lack of appreciation of the types of services provided and of the potential benefits to patients and family [78]. ESKD patient and family education about the benefits of hospice is important in optimal use of these services.

Underutilization is also likely to be due to eligibility requirements and the common misconception that dialysis patients must stop dialysis to receive hospice care. For example, eligibility for the Medicare hospice benefit in the United States is contingent on the terminal diagnoses for which hospice is engaged and patients may not receive two distinct Medicare benefits for the same illness. Thus, patients may not concurrently receive both hospice and ESKD benefits based on a diagnosis of ESKD alone. Therefore those with ESKD as the sole terminal diagnosis who desire hospice must forego their ESKD benefit and discontinue dialysis. A minority of patients with the terminal illness of ESKD who do not wish to discontinue dialysis may be fortunate enough to find a hospice willing to pay for dialysis as part of the hospice services being provided. Alternatively, dialysis patients with non-ESKD terminal

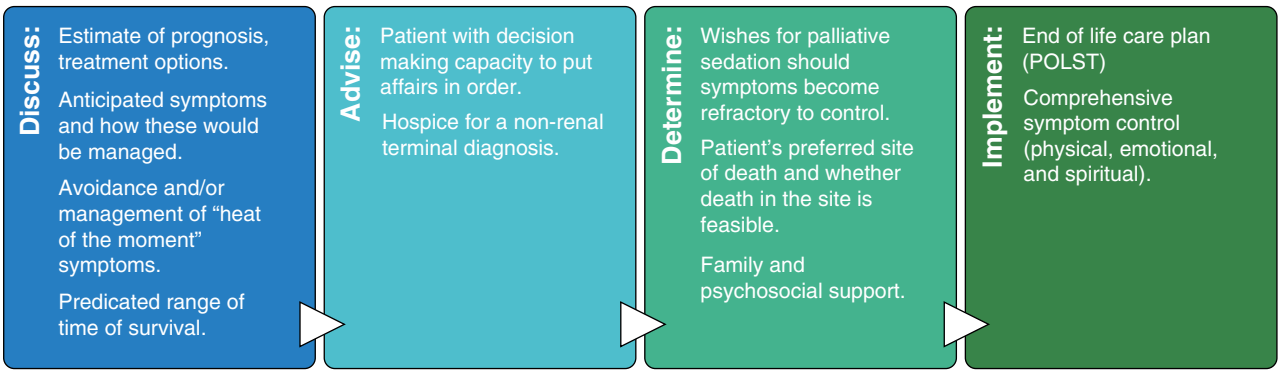

Figure 55.6 Treatment of respiratory tract secretions at the end of life. *Source:* Used with permission from Davison SN n behalf of the Kidney Supportive Care Research Group, University of Alberta and Alberta Health Services. Conservative Kidney Management: Patient Decision Aid. Alberta, Canada, 2016. CKM Pathway at http://www.CKMcom.care.

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diagnosis may retain their ESKD Medicare benefit and continue dialysis while they engage hospice. This diagnosis may be as simple as "failure to thrive."

Conclusion

Decision-making for patients and families facing ESKD can be challenging, particularly for older patients or those with complex multimorbidity whose prognosis and potential harms and benefits of dialysis are difficult to predict. However, it is critical that clinicians recognize the need to review all treatment options and provide their best advice based on patients' goals, values, and preferences and ensure the options for CKM and dialysis withdrawal are presented adequately. These care pathways will require a multidisciplinary care team well versed in symptom management and end-of-life care.

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Part 9

Transplantation

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56

Evaluation of the Living Donor Kidney

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Introduction

For patients who develop end-stage kidney disease (ESKD), compared to dialysis, kidney transplantation provides the lowest morbidity and greatest survival if a person is deemed healthy enough to receive one [1, 2]. The two sources of kidneys for transplantation are either a living or a deceased donor [1–3]. To meet the needs for transplant organs, live donation is an important aspect of transplantation, providing shorter time to transplantation and better clinical outcomes for recipients [2, 3].

The primary premise of living kidney donation is that the positive outcomes for the recipient and potential positive psychological outcomes for the donor outweigh the short- and long-term medical, psychosocial, and financial risks to the donor [4]. In this chapter we will discuss the assessment of a potential living kidney donor as this requires an appreciation of the existing literature on the risks involved with donation. Similarly, an understanding of the risks involved with donating a kidney is a key component to obtaining fully informed consent from the donor prior to surgery [4, 5].

The assessment of the potential living kidney donor includes (i) an evaluation of their fitness to undergo the operation, (ii) their fitness to live the rest of their life with only one kidney, and (iii) ensuring that the donor has no medical issues that could compromise the recipient in the event of donation. This chapter will not provide a list of tests to be performed but rather discuss the principles behind the potential donor's evaluation and some of the current evidence.

Assessment of the Living Kidney Donor's Fitness to Undergo the Operation

This part of the evaluation is really an assessment of the living donor's short-term surgical risks. The recently published Kidney Disease Improving Global Outcomes (KDIGO) Guidelines appropriately describe a living kidney donor nephrectomy to be equivalent to a noncardiac surgery of "moderate-size" [6].

Perioperative Mortality

The perioperative risk of death within the first 90 days has been estimated at 0.031% (3.1 in 10 000 donors) based on data on 80 347 living kidney donors in the United States between 1 April 1994 and 31 March 2009 [7]. Despite considerable changes in practice and donor selection over this 15-year period, there does not appear to be any change in the mortality rate [7]. The most common causes of death seem to be related to the development of pulmonary embolism and bleeding at the operative site, fundamentally diametrically opposite complications where the prevention of one may increase the risk of the other.

Perioperative Morbidity

Total rate of perioperative complications is estimated to be between 8% and 18%, with the relatively high variation likely reflecting differences in the method of ascertainment of complications [8–12]. The largest publication to

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date ($n = 69\,117$) had an incidence of 7.9%, but was limited by only collecting procedure-related complications [11]. Another prospective cohort study of 1042 living kidney donors in Canada and Australia who donated between 2004 and 2014 detected a complication rate of 13% [13]. With the recognition of the importance to monitor living kidney donor outcomes, some jurisdictions have attempted to keep a record of perioperative complications.

Venous thromboembolism (VTE) (including pulmonary emboli) occurs in less than 2% of cases, with increased awareness leading to recommendations of tailored VTE prevention depending upon the risk for the individual donor [14]. Risk stratification of a potential living kidney donor's VTE risk includes a preoperative evaluation of risk factors such as past history of VTE, older age, obesity, and medications [14]. Hemorrhage is the most common intraoperative complication but is also seen postoperatively.

Other common perioperative complications include urinary tract infections, gastrointestinal dysfunction, low-grade fever, wound infections, and pain [12]. The average length of stay following living kidney donation is dependent on the surgical technique (open versus laparoscopic) and local practices but averages 3–6 days. Risk factors for complications seem to include African Americans, predonation obesity, hypertension, hematological condition, and psychiatric condition [12].

In view of the extent of this operation, routine preoperative assessment should include an evaluation of the risks for cardiovascular, pulmonary, bleeding, anesthesia, and other perioperative complications. Besides smoking cessation, there is limited evidence to direct the most appropriate evaluations to make and practitioners should be guided by the information in this chapter and local practices.

Assessment of the Long-term Medical Outcomes for Living Kidney Donors

The decision to approve a potential living kidney donor to donate a kidney is predicated on understanding the long-term risk of living with a single kidney and assimilating that with the donor's preoperative characteristics that may add to these risks [6]. The difficulty with this process is that there still exists uncertainty about what precisely are the long-term risks of donating a kidney [15]. Below we will try to summarize the existing literature with respect to specific patient-level outcomes.

Blood Pressure

The kidneys are a key mediator of blood pressure control and so mechanistically it is easy to suspect that removal of one of two kidneys may lead to an increase in the patient's blood pressure [16]. Hypertension in turn can lead to progression of chronic kidney disease (CKD) and other adverse outcomes. A key study by Lentine et al. linked Organ Procurement and Transplantation Network (OPTN) records of all living kidney donors in the United States from a large, single national private US health insurer between October 1987 and July 2007 with a median follow-up of 7.7 years [17]. They described a prevalence of hypertension at 5 years of 17.8% and that for diabetes mellitus of 4.0% [17].

However, the main issue with the majority of studies to date on the long-term outcomes of people who donate a kidney is around what proportion of comorbidities that develop after donation is attributable to the donation itself, and how much would have happened as part of the normal aging process. The study by Lentine et al. compared the prevalence of the development of disease in the living kidney donor cohort with that from a general population cohort sampled from the National Health and Nutrition Examination Survey (NHANES) data (2005–2006 cohort) [17]. Using this methodology they still detected a higher prevalence of hypertension in the living kidney donor cohort than their general population cohort, but with similar prevalence of diabetes. This still raises the question on whether this comparator group is the correct one, as living kidney donors undergo rigorous testing prior to donating to ensure that they are very healthy.

A previous systematic review and meta-analysis assessed blood pressure changes in studies that included healthy nondonor controls along with living kidney donors [18]. Their pooled estimate of four trials with controls at least 5 years after kidney donation revealed a significantly higher systolic blood pressure of 6 mmHg (95% confidence interval [CI] 1.6–10.5) compared to a 4 mmHg (95% CI 0.9, 6.7) higher diastolic blood pressure in the donors from the five trials identified [18]. A more recent systematic review still identified a higher diastolic blood pressure in donors compared to controls but no difference in systolic blood pressure or the development of hypertension [19].

Proteinuria

Proteinuria in the general population is a predictor of renal outcomes, cardiovascular disease, and mortality [20]. Amongst living kidney donors it has been noted to occur in up to 20% on follow-up [21–23]. In a systematic review and meta-analysis of studies the incidence of proteinuria was 12% (95% CI 8–16%) amongst 42 studies with 4793 living

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kidney donors followed up for an average of 7 years postdonation [23]. In the small number of studies that included a control comparator group, there also was found an increased amount of proteinuria (mean difference of 66 mg/day (95% CI 24–108) at an average of 11 years postdonation) [23]. However, the prognostic significance of this increased proteinuria in living kidney donors is unknown and may not necessarily be similar to that seen in the general population.

Cardiovascular Disease

As CKD, even from a glomerular filtration rate (GFR) <75 ml/min/1.73 m^2, has been associated with cardiovascular disease, it has been a concern that this may be increased with donating a kidney [24]. There have been four studies to date that have examined this with a comparator group of healthy controls. While one study did document an increased incidence of cardiovascular mortality compared to the control population, the other three studies did not and a meta-analysis of the four studies showed no significant difference in this outcome amongst living kidney donors [19, 22, 24–27].

Survival

The initial investigations into survival amongst living kidney donors were reassuring, with the most notable and often quoted study being from the Swedish group [28]. This study followed a cohort of 430 living kidney donors from Stockholm, Sweden between 1964 and 1994, and compared their survival with that of the general population. They found a 29% (95% CI 20–38%) better survival amongst living kidney donors (attributed to the careful selection process donors undergo compared to the general population), a finding that reassured many in the transplant community at the time. In a single-center study of 3698 living kidney donors from the University of Minnesota, there were 268 deaths in the follow-up period with similar survival rates when compared to the general population [22].

With increasing recognition that the general population may not be an appropriate comparator group, four publications have subsequently been published with healthy controls as the comparator group. The healthy controls were generated by selecting a "healthy" subgroup of an existing cohort, e.g. Segev et al. used the NHANES III cohort and excluded those that had existing kidney disease, diabetes mellitus, hypertension or ischaemic heart disease [7]. This information was attained from the previously obtained 30 screening questions performed at baseline for NHANES III. Two of the other four studies also found a higher survival amongst living kidney donors compared to their "healthy" control group [25, 29]. There was one study from Norway, where all kidney transplants for the country are performed in a single transplant unit in Oslo, that followed up 2269 living kidney donors [26]. The authors matched the living donors to people identified from a preexisting cohort identified from a population-based survey performed between 1984 and 1987 in Norway. They only included those people who had normal blood pressure, body mass index (BMI) <30 kg/m^2, and self-rated their health as "good" or "excellent." They demonstrated a statistically significant increase in mortality amongst the living kidney donors compared to the "healthy" controls, with a hazard ratio of 1.30 (95% CI 1.17–1.88). Notably, they did not detect this increased mortality rate until after 10 years of follow-up, which is longer than most existing studies. A meta-analysis of all four studies showed no significant difference in survival though CIs remain a little wide and there was a trend toward improved survival [19].

End-stage Kidney Disease

In the study from Norway, nine of the living kidney donors developed ESKD, resulting in a crude incidence of 302 per million person years [26]. This compared to 100 per million patient years for the general population of Norway and a hazard ratio of 11.38 (95% CI 4.37–29.63) compared to the matched "healthy" controls. Muzaale et al. published on the US OPTN database, identifying 96 217 living kidney donors between April 1994 and November 2011 [30]. They compared outcomes with a matched cohort of "healthy" controls generated from the NHANES III dataset and demonstrated a cumulative incidence of ESKD 15 years postdonation of 30.8 per 10 000 donors versus 3.9 per 10 000 healthy nondonors, $P < 0.001$ [30]. Similar to the Norwegian study, they also demonstrated that living donors still had a statistically significant lower incidence of ESKD than the general population. On systematic review and meta-analysis, donors were found to have a significantly increased incidence of ESKD (relative risk [RR] 8.83, 95% CI 1.02–20.93) [19].

Pregnancy-related Complications

There have been three publications on pregnancy-related outcomes in living kidney donors [31–33]. The most recent publication demonstrated a statistically significant increase in the incidence of gestational hypertension or preeclampsia in 181 living kidney donors compared to 788 matched healthy women (odds ratio [OR] 2.4, 95% CI 1.2–5.0) and absolute incidence of 11% versus 5%. This finding was

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maintained on meta-analysis [19]. No significant increased incidence could be found with the development of low birth weight or preterm birth.

Psychosocial Considerations for Living Kidney Donors

All potential living kidney donors should have a detailed psychosocial evaluation to ensure that their risk of adverse psychological outcomes can be estimated and a plan devised to minimize them and manage any that may occur. Discussion and consideration of how the potential living kidney donor may react if there is a bad perioperative outcome should be made. A wide variation currently exists in how this evaluation is made with no preferred method proven to be more effective than another [34, 35].

Most studies of the psychosocial outcomes of living kidney donors have generally shown positive findings with minimal adverse outcomes. A recent study examined prospectively a cohort of 193 living kidney donors and 20 healthy controls, and measured an array of psychosocial outcomes predonation and at 1, 6, 12, and 24 months postdonation [36]. They used validated questionnaires to measure these outcomes. Overall, there was the development in a small proportion of donors of new adverse psychosocial outcomes but not significantly more than in the healthy controls. It was also noted that a proportion of donors did demonstrate an improvement in their psychosocial wellbeing postdonation. These findings were supported in a systematic review and meta-analysis that examined 10 studies that used the short-form 12 or short-form 36 health survey to measure quality of life in donors and controls [19]. This study found no important or statistically significant difference in mental or physical scores between the two groups.

Selection of the Living Kidney Donor

The evidence to date still maintains some uncertainty about the long-term complications following living kidney donation. With the information above noted, plus the knowledge that CKD does lead to increased cardiovascular morbidity, plus cardiovascular and all-cause mortality, the evaluation of potential living kidney donors should be performed with this in mind. KDIGO guidelines nicely describe the long-standing intuitive assessments that have been made to date when deciding on a potential living kidney donor's suitability to donate (Figure 56.1). The potential donor's risks are quantified and if the risks are above a certain threshold they are not accepted and if they are below a certain threshold then they are able to donate. The issue with this is that it is very hard to quantify an individual's overall risk and it is also hard for a transplant unit to agree on a threshold level for all types of potential donors.

Kidney Function

The lack of adequate evidence to fully quantify the risk for a potential donor has continued to make this process an art

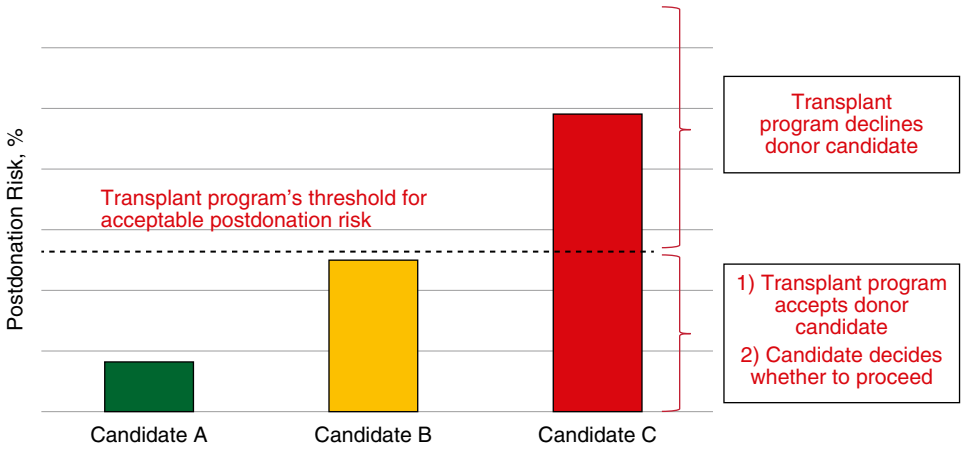

Figure 56.1 Framework to accept or decline donor candidates based on a transplant program's threshold of acceptable postdonation risk. The decision by the transplant program to accept or decline a donor candidate is grounded on whether an individual's estimated postdonation risk is above or below the threshold set (dotted line) by the transplant program. The threshold may vary across transplant programs, but the same threshold should apply to all donor candidates at each program. For example, candidate A (green) would be acceptable because the estimated projected postdonation risk is far below the threshold. Candidate B (yellow) could be accepted with caution because the estimated projected postdonation risk is close but below the threshold, and candidate C (red) would be unacceptable because the estimated postdonation projected risk is far above the threshold. *Source:* Lentine et al. [6].
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form rather than a pure science. Kidney function is probably the one area with the most information to guide our decision-making. Many jurisdictions have traditionally set a threshold level of kidney function below which a potential donor would be deemed unacceptable for donation, for many this has been 80 ml/min/1.73 m^2 [37, 38]. The two main concerns are leaving the donor with reduced kidney function that in turn leads to adverse outcomes for the donor, in addition to leaving the kidney transplant recipient with inadequate kidney function for long-term benefits. While the donor has their kidney function immediately postoperatively reduced to approximately 50% of the predonation level, with compensatory hyperfiltration the donors usually finishes with 30% reduction in kidney function compared to predonation [21–23]. The rationale behind this threshold is largely based on tradition and dogma rather than evidence [39].

KDIGO described the concept of lifetime risk, such that the younger the living donor the longer their expected life expectancy and so the greater their exposure to risk. This has been developed further by the Chronic Kidney Disease Prognosis Consortium, who focused on the development of ESKD [40]. They combined data from multiple North American general population studies, with almost five million participants, to develop a risk calculator to estimate the long-term incidence of ESKD. They propose that this can be used in the assessment of potential living kidney donors to estimate their 15-year and lifetime risk of developing ESKD if they were to not donate a kidney. As you can see from Figure 56.1, the younger the donor, the greater the cumulative risk for ESKD. The proposal is that a transplant unit can decide on what threshold risk they would accept for a potential living kidney donor and if their risk is above this threshold then decline them for donation. Ongoing efforts to better quantify risk in this way may lead to a more transparent and equitable process.

One of the things that this equation does not take into account is the amount of added risk the individual will have if they were to donate a kidney – attributable risk. Grams et al. attempted to provide an estimate of the attributable risk of donation by applying the same equation to almost 53 000 previous living kidney donors in the United States and comparing the 15-year predicted incidence of ESKD with the actual incidence. Here they found a 3.5- to 5.3-fold higher observed incidence of ESKD compared to that predicted by their equation, potentially providing us with a means to estimate attributable risk for the donation process. These equations need to be validated in other populations before being used outside of North America.

The KDIGO Guidelines have recommended against a single threshold for acceptable kidney function for all potential donors [6]. Instead they have set a few thresholds: >90 ml/min/1.73 m^2 being acceptable for donation, <60 ml/min/1.73 m^2 being unacceptable for donation, and 60–90 ml/min/1.73 m^2 being up for discussion. This would be dependent on the individual's longer term risk of ESKD dependent upon their baseline demographics and comorbidities plus the added attributable risk of donation. For example, an older potential donor has a lower lifetime risk of ESKD and therefore it is possible to accept a lower level of kidney function predonation.

This example of predicting the lifetime risk of kidney failure in a potential living kidney donor needs to be applied to multiple clinical outcomes in every potential donor: cardiovascular disease, all-cause mortality, diabetes, mental illness, quality of life, and others. Hence the complexity of this evaluation process and the difficulty in describing the evaluation in concrete and transparent terms for each individual donor evaluation.

Transmission of Disease from the Donor to the Kidney Transplant Recipient

The other aspect of the evaluation of a potential living kidney donor is to ensure that they do not have a disease that could be transferred to the kidney transplant recipient. Especially in the context of immunosuppression, any such condition transmitted may have dire consequences. These diseases are typically neoplastic or infective. Screening for cancers according to local guidelines is recommended [6]. If the potential donor has a history of neoplasms, there have been guidelines developed with respect to years of remission prior to being deemed suitable for donation. These are largely based on case reports, case series, cohort, and registry studies [41]. The Organ Procurement and Transplantation Network Disease Transmission Advisory Committee Malignancy Subcommittee published different neoplasms into six levels of risk stratification which may be used as a guide to decision-making but it should be remembered that further data is still required to confirm this classification system [42].

Infections also need to be screened for, with some infections being "acceptable" as potential/likely transmissible agents, e.g. cytomegalovirus (CMV) and Epstein-Barr virus (EBV) (potentially) [6]. More recently, with the development of successful curative treatments for hepatitis C, it is being mooted that this may also become an acceptable infection for a donor to have, though in a living kidney donor attempts should be made to cure this prior to donation [43]. There are some other infections which continue to be (relative/absolute) contraindications for donation: human immunodeficiency virus, tuberculosis, hepatitis B,

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and syphilis [6]. Consideration for local endemic infections or those of the potential donor's original place of residence needs to be made [44].

Recent Trend Toward Accepting Living Kidney Donors with Medical Conditions

For much of the time since the first living kidney donation in 1952, donors have been selected based on a very high standard of good health. As we have become more comfortable with this procedure, confident in our belief that donors are not significantly affected by donation, and continue to have a shortage of deceased kidney donors, there has been an increasing tendency to accept donors with some conditions that may previously have precluded them from donation [45].

In the ANZDATA Living Kidney Donor Registry it was noted that in the period between 2004 and 2012 there were 2932 donors in Australia and New Zealand [45]. When some of the living kidney donors' demographic details were compared to national guidelines on selection of living kidney donors, it was identified that 26% had at least one relative contraindication to donation and 9% had at least one absolute contraindication to donation. This included donors that had hypertension (20%), diabetes (0.3%), and impaired glucose tolerance (2%) at the time of donation.

Similarly in the United States, Muzaale et al. demonstrated that amongst the 96 217 living kidney donors between 1 April 1994 and 30 November 2011, 25.2% had a BMI > 30 kg/m^2, 9% had a systolic blood pressure over 140 mmHg, and 24.2% were smokers at the time of donation [30]. The fact that we are accepted donors that we previously were not suggests that we need to consider this when reviewing data on long-term outcomes of living kidney donors. Such long-term outcomes may only be applicable to similarly healthy donors to our historical donors.

Informed Consent

An essential component of any medical procedure is to ensure that the person is adequately informed about what the procedure entails and understands the risks involved. For living kidney donation these risks include short-term (those within the first 90 days of the donation) plus long-term risks (for the rest of the donor's life). While the short-term risks are relatively well defined, there is still a large amount of uncertainty with the long-term outcomes. This. however. does not discount our ability to present the current level of evidence that exists (along with the uncertainty) and behooves us to ensure we continue to grow the evidence.

Postdonation Follow-up

Traditionally, living kidney donors have not routinely been followed-up by kidney transplant units and are discharged back to their primary physician after postoperative recovery is assured. This is in keeping with the message that we try to convey to donors – that they are still healthy postdonation. However, it has led to the uncertainty of precisely what the long-term risks are and recent evidence suggests that there may be some increased risk, albeit small in absolute terms. Maybe because of this uncertainty, the potential of increased risk of poor outcomes, and the premise that the transplanting team has some responsibility to provide life-long care of a kidney donor's remaining kidney function, many units are providing ongoing follow-up of living kidney donors. This is often in the form of an annual review which would include blood pressure measurement, serum creatinine, estimation of albuminuria, and emphasis on healthy lifestyle behaviors.

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57

The Impact of Deceased Donor Quality and Outcomes after Kidney Transplantation

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Introduction

Although kidney transplantation is the standard of care for patients with end-stage renal disease (ESRD) [1, 2], there is a worldwide shortage of organs available for kidney transplantation. In the United States, despite a kidney transplant waiting list of nearly 90 000 candidates, there are fewer than 20 000 kidney transplants performed annually [3]. Limited deceased donor pools serve as a barrier to transplantation throughout many other countries as well [4–6]. Attempts have been made to mitigate the scarcity of available organs and enlarge the donor pool by expanding acceptance criteria for potential deceased kidney donors (Figure 57.1.), including utilization of expanded criteria brain dead donors (ECD), the Kidney Donor Profile Index (KDPI) >0.85, and donation after cardiac death (DCD) as well as donors labeled as increased risk for infectious diseases and those with documented infections, such as hepatitis C virus (HCV) and/or human immunodeficiency virus (HIV).

However, the quality of the deceased donor kidney has been shown to influence both patient and graft survival for the recipient [7, 8], and as such must be considered during the selection of both kidney transplant recipients and donors. Consequently, standardized assessments of donor quality have been established, including the designation of ECD and KDPI scores. Transplant provider understanding of donor quality and subsequent risks and potential outcomes for recipients is paramount, as appraisal and approval of donors and recipients for transplantation lies with the transplant team of surgeons and nephrologists (Table 57.1).

Pathophysiology of Deceased Donors

Donation after Brain Death

Brain death is diagnosed as lack of responsiveness or coma accompanied by apnea and an absence of brain stem reflexes, despite standardized conditions (e.g. normothermia, lack of electrolyte/acid-base/endocrine disturbance, blood alcohol content <0.08, systolic blood pressure greater than 100 mm Hg, and lack of medications that cause central nervous system depression) [9]. Brain death occurs after severe brain injury, which causes increased intracranial pressure and cerebral edema, leading to decreased brain perfusion and ultimately the termination of cerebral blood flow [10]. Large animal models have demonstrated the physiologic responses that occur following brain death, such as hypertension and bradycardia, which are then followed by hyperdynamic state due to catecholamine surge [11]. After this initial increase, there is a drop in the catecholamine level, which then leads to cardiovascular instability and poor visceral perfusion [11]. Following brain death, there is also a shift from aerobic to anaerobic metabolism, evidenced by elevated serum lactic acid levels [11]. Hormonal changes due to disruptions in the hypothalamic-pituitary axis also occur, including the development of diabetes insipidus and decreased cortisol levels, which further propagate hemodynamic instability and inflammatory responses [11]. The inflammatory response also leads to endothelial, complement, and coagulation pathway activation, which can all lead to organ damage [11]. Furthermore, the diagnosis of brain death may lag behind these pathophysiological changes, leading

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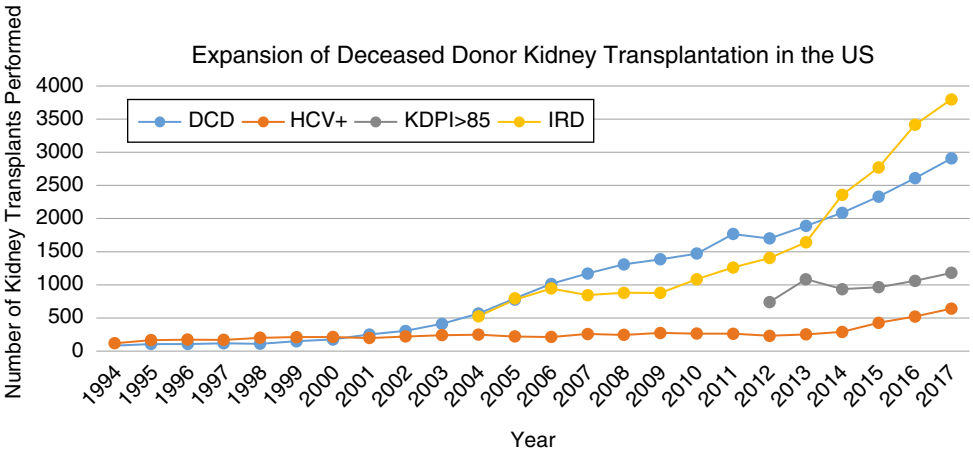

Figure 57.1. Utilization of deceased donor kidney transplantation in the United States, based on OPTN data as of 3 August 2018.

to organ compromise prior to confirmation of brain death [11]. These pathophysiologic changes further highlight the need for transplant surgeons and physicians to critically evaluate organ quality prior to transplantation.

Donation after Cardiac Death

DCD donors are typically those who do not meet brain death criteria, but for whom further medical intervention is deemed futile [10]. DCD donation is not associated with an inflammatory response as robust as that elicited by donation after brain death (DBD) [11]. However, there is a longer warm ischemia time associated with DCD, resulting from the time period between withdrawal of respiratory/circulatory support and time of death [12]. The prolonged warm ischemia can then lead to higher rates of primary nonfunction and delayed graft function (DGF) in kidney transplant recipients [11]. As a result, there are established maximum warm ischemia times after which organ procurement is not typically pursued. The warm ischemia time permissible for kidney procurement varies by country, with a 60-minute time period commonly used in the United States, a 90-minute period used in Australia, and a 1–4-hour period used in the UK [13, 14].

Expanded Criteria Donors/High Kidney Donor Profile Index (KDPI > 0.85)

Epidemiology

In Spain, where living donor kidney transplantation accounted for less than 1% of all kidney transplants, there was a great need to improve the utilization of deceased donor kidneys for transplantation [15]. As such, they began to transplant kidneys from older donors and those with hypertension, aiming to decrease their discard rates. Over the course of a decade, Spain was able to increase their organ donor annual rate from 14 donors per million population pmp (per million population) to 34 donors pmp as of the early 2000s [15, 16]. Following suit, in the United States, the Kidney Work Group created the Crystal City Kidney proposal for determining ECD status in 2001, in which they compared the discard rate for older donors in the United States to the practices in Spain [17]. The authors found that if the utilization of kidneys recovered from donors over the age of 45 in the United States mirrored the trends in Spain, this would correlate with an increase in the rate of deceased donors in the United States by 38% [17]. The following year, a definition was put forth describing ECD in the United States, including characteristics that were associated with a 1.7-fold increased relative risk for allograft loss in the recipient [18, 19]. Then in 2009, KDPI was introduced by Rao et al. in an attempt to further quantify the risk of graft loss due to donor characteristics, yielding a percentile which corresponded to the predicted allograft longevity in lieu of the dichotomous ECD status [20].

Diagnosis

The characterization and determination of "marginal" or "expanded criteria" donors have undergone multiple iterations over time. Ojo et al. defined marginal donors as those with one or more of the following characteristics: age over 55 years, greater than 10-year history of hypertension or diabetes mellitus, DCD donation, or cold preservation time of greater than 36 hours [21]. Port et al. established ECD donors as those with a relative risk of graft loss greater than 1.7 compared with standard criteria brain dead donors [18]. The authors described standard criteria donors (SCD) as those who were 10–39 years of age, had terminal serum

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Table 57.1 Deceased donor kidney transplantation (KT) recommendations.

Deceased donor classification	Recommendation	Certainty of evidence	Strength of recommendation
Expanded criteria/high KDPI donors	We suggest KT with high KDPI organs for older recipients, or those at centers with longer waiting times, or patients with both older age and longer waiting times due to the survival benefit derived compared with continuing to wait for a low-KDPI organ.	Low	Weak [33]
Infectious risk donors	We suggest KT with IRD kidneys for older candidates, with higher PRA, previous KT, or those who face long waiting times due to the observed survival benefit compared with declining IRD kidneys.	Low	Weak [39]
HCV+ donors	We suggest KT with HCV+ organs for HCV+ recipients, followed by post-transplantation DAA therapy. Likewise, there may be a role for HCV+ KT for HCV- recipients.	Low	Weak [73]
HIV+ donors	We suggest KT with HIV+ organs for HIV+ recipients. However, in the United States this is currently limited to research protocols. Recipients should have a CD4 count greater than 200/μl and be on a stable antiretroviral regimen, with viral load <50 copies/ml. Among younger HIV recipients with low panel reactive antibodies, patient and graft survival is similar to HIV− recipients.	Low	Weak [81, 107]
Donation after cardiac death	We suggest the use of DCD organs for kidney transplantation. However, increasing donor and recipient age, prior transplantation, and increased cold ischemia time are associated with poor graft and patient survival among recipients of DCD kidneys.	Low	Weak [108]

DAA, direct-acting antiviral; DCD, donation after cardiac death; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IRD, infectious risk donor; KDPI, kidney donor profile index; KT, kidney transplantation; PRA, panel reactive antibody.

creatinine 1.5 mg/dl or less, had cause of death other than cerebrovascular accident, and had no history of hypertension [18]. Based on these findings, the US Organ Procurement and Transplantation Network (OPTN) created the designation of ECD donors as brain death donors over the age of 60 years, or over the age of 50 with two of the following: history of hypertension, serum creatinine 1.5 mg/dl or greater, or cerebrovascular accident as cause of death [19].

Rao et al. further delineated the risk of graft loss according to deceased donor characteristics through the creation of the kidney donor risk index (KDRI), which was developed among a cohort of donors in the United States from 1995 to 2005 transplanted into ABO compatible, first-time solitary kidney recipients [20] (Table 57.2). Importantly, the KDRI accounts for type of donor death, with a higher risk index associated with cardiac death compared to brain death. The KDRI, which gives the relative risk of graft loss, is then remapped and given a percentile, also known as KDPI, such that a score of 10 indicates that the allograft will likely last longer than 90% of other kidney allografts transplanted in the same year (OPTN website). Furthermore, kidneys with KDPI of 0.85 or greater, thought to be similar to ECD kidneys, are usually reserved for recipients with high-risk features ([22], OPTN website). Additionally, with the advent of KDPI, which describes both DCD and DBD donors, ECD is now also used to describe donors following cardiac and brain death, and the ECD designation now is more synonymous with "marginal" donors.

Table 57.2 Characteristics of deceased donors included in calculation of kidney donor risk index [94].

Age
Height
Weight
Ethnicity (African American)
History of hypertension
History of diabetes
Cause of death (cerebrovascular accident)
Serum creatinine
Hepatitis C virus status
Donation after circulatory death status

Source: Based on A Guide to Calculating and Interpreting the Kidney Donor Profile Index (KDPI), 23 March 2020, US Department of Health and Human Services.

Prognosis

Although ECD kidneys pose a greater risk of graft loss based on the nature of the designation, the prognosis for recipients

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of ECD kidneys is not uniformly poor. Ojo et al. found a survival benefit for transplant recipients of marginal kidney donors compared with remaining waitlisted on dialysis [21]. Alternatively, Saidi et al. found that recipients of ECD kidneys had longer lengths of stay, higher readmissions, and increased DGF compared with SCD recipients [23]. The authors also noted decreased graft survival among ECD recipients after a mean follow-up of 50 months, with significantly increased graft loss noted at 2 years post transplant [23]. In reality, not all aspects of ECD kidneys carry the same weight in respect to risk of graft loss, and therefore selecting the best recipient for an ECD kidney is pivotal. Several studies haves shown that older donor age was associated with increased DGF and poor graft survival among ECD donors [21, 24]. Stratta et al. stressed the importance of recipient selection for ECD kidneys and demonstrated no statistically significant differences in ECD and SCD outcomes, including DGF, acute rejection, and 4-year patient and graft survival [25]. Furthermore, additional information from kidney biopsies, such as the severity of histological damage, may be useful to aid in the determination of organ suitability for transplantation among deceased donors meeting ECD criteria [26].

The United Network for Organ Sharing (UNOS) ECD designation may not be uniformly applicable throughout the world, and when employed in different patient populations may yield different results. In Japan, Nakagawa et al. found that using the UNOS ECD classification categorized 84% of their deceased donors as ECD, despite no differences in outcomes between SCD and ECD donor recipients [6]. A study from Korea showed that ECD recipients had increased DGF and longer wait times on dialysis but no differences in patient or graft survival compared to both SCD recipients of DDKT (deceased donor kidney transplant) and living kidney donor recipients [27]. Similarly, Palkoci et al. found no difference in long-term patient and graft survival for ECD donor recipients compared with SCD recipients despite poorer graft function in the first 6 months post transplant [28]. In Poland, authors found an increased risk of graft failure but similar patient survival and DGF using ECD donors compared with SCD donors [29].

Since the KDPI was developed to predict which deceased donor kidney transplants were predisposed to allograft failure on the basis of donor characteristics, it is not surprising that as the KDPI increases, graft failure rates also increase (Figure 57.2.) (OPTN website). Recipients of kidneys with low KDPI (≤0.20) are expected to have a mean half-life of 11 years, nearly the same expectancy as recipients of living donor kidneys, while high KDPI kidneys have an estimated graft life of about 5.5 years [30]. Consequently, kidneys with a KDPI of >0.90 had a discard rate of over 60% in the United States between 2001 and 2012 [30]. Furthermore, Bae et al. demonstrated that in the KDPI era, there was a paradoxically higher discard rate for kidneys meeting the conditions for ECD [31]. Other countries have also utilized KDPI to assess deceased donor quality, and in Spain although the SCD/ECD classification was not predictive of graft function, increased KDPI was associated with poor

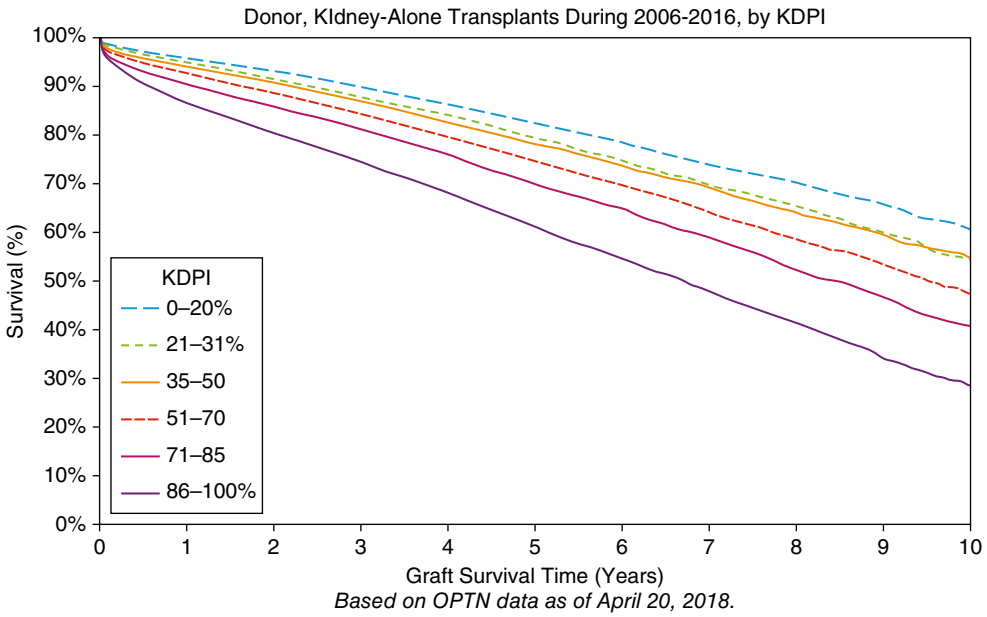

Figure 57.2. Kaplan–Meier graft survival estimates for adult deceased donor kidney transplant recipients, stratified by KDPI [94]. *Source:* A Guide to Calculating and Interpreting the Kidney Donor Profile Index (KDPI), 23 March 2020, US Department of Health and Human Services.

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graft survival [32]. However, despite the increased risk of allograft loss with high KDPI kidneys, Massie et al. found a survival benefit for receiving high KDPI kidneys compared with remaining on the waitlist for some patient subgroups, including diabetic recipients over the age of 50 years listed at centers with long waiting times [33].

Treatment

Compared with IL2 receptor antibodies (IL2RA), antithymocyte globulin (ATG) has been associated with decreased acute rejection among recipients of ECD kidneys [34]. Furthermore, for ECD kidney recipients who were African American, had high panel reactive antibodies (>20%), or had previous kidney transplants ATG was also associated with improved graft survival compared with IL2RA [34]. Alternatively, another study compared outcomes between ATG and daclizumab in this patient population and found no statistically significant differences in patient or graft survival [35]. It should be noted, however, that daclizumab is no longer used in the United States. Maintenance immunosuppression for ECD kidney recipients has not been established through randomized trials, but regimens that avoided calcineurin inhibitors (CNIs) were originally proposed to avoid potential nephrotoxicity, although these regimens have been associated with increased risk of acute rejection [36, 37]. Therefore, standard triple therapy maintenance immunosuppression is recommended for recipients of ECD kidneys, with CNIs, mycophenolate mofetil (MMF), and steroids. However, reduced CNI exposure via lowered target serum levels may be beneficial in this recipient population [36].

Donors Labeled High Infectious Risk

Epidemiology

In 1994, the US Centers for Disease Control (CDC) established guidelines to prevent potential unknown transmission of infectious diseases, such as HIV, through organ transplantation [38]. They recommended the implementation of certain exclusionary criteria for organ donation, including previous intravenous drug use, incarceration, men who have sex with men, and prostitution, unless the risk of infectious disease for the recipient was deemed less than the risk of not undergoing transplantation (Table 57.3) [38]. These "CDC high risk donors," also known as infectious risk donors (IRDs), represent donors with no documented infection despite behavioral risks for infection and accounted for 10% of deceased donors in the United States as of 2011 [39]. However, the disease transmission risk is generally low, with the risk of HIV or HCV transmission from high-risk donors estimated to range from 0.09 to 300.6 per 10 000 donors, based on serologic testing [40]. In reality, the risk of disease transmission following transplantation from IRDs is exceedingly low, with a transmission risk of 46 per 100 000 IRD transplant recipients compared with 2.4 per 100 000 transplant recipients of all donor types [41]. In fact, assuming a 100% mortality following HIV transmission, the predicted mortality risk due to HIV transmission following IRD kidney transplantation has been shown to be comparable to the mortality risk associated with living kidney donation [41]. Likewise, the incremental mortality risk associated with IRD kidneys is very small compared with the risk of waitlist mortality [41]. Additionally, there has only been one documented deceased kidney donor transmission of HIV in the United States since 1988 after more than 200 000 deceased donor transplants have been performed [41].

Diagnosis

Donors at high risk for infectious diseases were described by the exclusionary criteria created and distributed by the CDC in 1994, as shown in Table 57.3 [38]. Although these donors are tested for HIV and HCV prior to donation, the window period, or time between disease acquisition and detection via serology, allows for potential transmission of infectious diseases to the recipient [42]. Using enzyme-linked immunosorbent assays (ELISA), the window period is typically 22 days for HIV and 66 days for HCV, while using nucleic acid testing (NAT) decreases the window period to 9 days for HIV and 3–7 days for HCV [42–46]. Therefore, given the smaller window period available with NAT testing, there is a decreased risk of infectious disease

Table 57.3 High-risk criteria, described by CDC in 1994 [38].

Behavior/history exclusionary criteria/high-risk criteria
Men who have had sex with another man in the last 5 years
Persons reporting nonmedical intravenous, intramuscular, or subcutaneous drug use in the last 5 years
Hemophilia or other clotting disorders, or those who have received clotting factor concentrates
Persons who have engaged in sex in exchange for money or drugs in the last 5 years
Persons who have had sex in last year with anyone listed above, or with anyone known/suspected to have HIV
Persons who have been exposed to known or suspected HIV in the last year
Inmates of correctional facilities

Source: Modified from Centers for Disease Control and Prevention [38].

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transmission from high-risk donors compared to earlier eras secondary to the improved testing [47]. Based on NAT testing, the risk of HIV transmission during the window period is estimated to be 0.04–4.9 per 10 000 donors, while the risk of HCV transmission is 0.027–32.4 per 10 000 donors [40]. The risk for disease transmission is highest among intravenous drug users, and lowest in hemophiliacs and those who were previously incarcerated [48, 49].

The importance of NAT testing for infectious diseases among blood and tissue donors has become increasingly apparent over the past decade. Roth et al. administered an international survey of 37 countries on NAT screening for whole blood and platelet donors, finding that over a 10-year period, 300 million donors were screened for HCV and HIV [50]. Of those donors, nearly 1000 were NAT-only positive, which would have been missed by other serologic screening methods [50]. Similarly, in 2015, UNOS mandated the inclusion of NAT testing for reporting HCV status for transplant donors, which correlates with a 10-fold decrease in the risk of unintended transmission of HCV at time of transplant [46].

Prognosis

Studies have shown that recipients of IRD kidneys have had similar short-term patient survival compared to recipients of standard risk kidneys [51–53]. This is not surprising given that these high-risk donors are typically younger, with lower terminal serum creatinine, and are less likely to have other comorbidities such as hypertension [45, 54]. However, at longer term follow-up, higher risks of mortality have been reported for recipients of IRD kidneys [55]. Despite the majority of studies yielding positive reports regarding the outcomes following the transplantation of kidneys from IRDs, kidneys from IRDs are one-third less likely to be utilized for transplantation [54].

Recipient selection for IRD kidneys is pivotal. Chow et al. developed a Markov model to aid in the decision-making process, finding that recipient age, sensitization as measured by panel reactive antibodies, previous transplant, and waitlist times were predictive of survival differences [39]. Furthermore, recipient education and understanding of IRD kidney donation is also critical. A qualitative study that sought to capture patients' understanding of high-risk organs demonstrated that many candidates were confused about what constituted CDC high risk [56]. Although the waitlist candidates had a general lack of understanding, the authors also established the candidates' interest in learning more about high-risk donors [56]. Informed consent for IRDs is therefore critical, ensuring that patients understand the risks associated with these organs, and consequently in the United States the OPTN mandated a separate consent form for recipients of these donor organs [57]. Another qualitative study confirmed candidates' trepidation regarding high-risk donor kidneys due to concerns of disease transmission, finding that patients' feelings toward these organs were negative and that they were often viewed as "last resort" options if death was forthcoming [42].

Treatment

Induction immunosuppression does not need to be specifically tailored for recipients of IRD kidneys on the basis of their infectious risk. The induction agent selection should be based on the recipient characteristics. Standard triple therapy maintenance immunosuppression, with CNI, MMF, and steroids, should follow induction therapy.

Donors with Hepatitis C

Epidemiology

In part due to the opioid crisis yielding higher numbers of overdose deaths and also secondary to the introduction of direct-acting antiviral (DAA) agents, there has been an increase in the use of HCV+ deceased donors since 2014 [58]. Li et al. demonstrated that the number of transplants from HCV+ donors in the United States increased from 247 in 2013 to 520 in 2016 [58]. Although this represents improvement, a great need still remains to expand the utilization of HCV+ organs, as Kucirka et al. demonstrated that the discard rate for HCV+ kidneys was nearly three-times the discard rate for HCV− kidneys [59].

Diagnosis

HCV status is confirmed via antibody and NAT testing. Historically, HCV+ kidneys were reserved for HCV+ recipients who were viremic to reduce the possibility of worsening the HCV disease or disease progression. However, with DAA therapy, HCV+ organs are no longer limited to viremic HCV+ recipients. Recently, Gentile et al. demonstrated that genotyping of HCV+ deceased donors was possible, and may help in the future to guide decision-making regarding recipient selection and treatment regimens [60].

Prognosis

Maluf et al. demonstrated that among HCV+ transplant recipients, those who received HCV+ donor kidneys had decreased waiting times (mean time of 440.5 days vs. 735.0 days) but also poorer patient and graft survival,

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compared with their counterparts receiving HCV− organs [61]. Similarly, Cohen et al. described an increased risk of death and allograft loss among HCV+ recipients of HCV+ kidneys, compared to recipients of HCV− organs [62]. Other studies have demonstrated acceptable graft survival for HCV+ recipients (90% at median follow-up 14 months, compared with 92% for HCV+ recipients of HCV− organs) [63]. When assessing long-term outcomes, Morales et al., in their single-center study, found that there was no increased risk of graft failure at 5 and 10 years post-transplant, death or severe liver disease among HCV+ recipients of HCV+ donor kidneys compared to HCV+ recipients of HCV− kidneys [64]. However, among HCV+ recipients, Kucirka et al. found an increased risk of being added to the liver transplant waitlist for those who received HCV+ kidneys compared with recipients of HCV− kidneys, although the difference in listing rates between the two groups was less than 2% [65]. Sawinksi et al. found that there was no difference in response to DAA therapy among HCV+ recipients of HCV− and HCV+ kidney transplants, while recipients of HCV+ organs were afforded shorter wait times to transplantation, leading the authors to advocate for the use of HCV+ organs and post-transplant DAA therapy [66].

Given the success of DAA therapy for HCV, some have also promoted the use of HCV+ organs for HCV – recipients. Gupta et al. found that for kidney transplantation among HCV+ donors and HCV− recipients, seroconversion occurred for roughly half of the recipients [67]. Although graft survival was worse among these recipients compared to their matched counterparts receiving HCV− organs, graft survival did not differ on the basis of seroconversion, leading the authors to believe that other factors aside from HCV status may have contributed to the differences in graft survival for recipients of HCV+ kidneys [67]. Additionally, Goldberg et al. conducted a pilot study among HCV− recipients of HCV genotype-1 viremic donor kidneys, finding that despite detectable viral load at 3 days post-transplant, all recipients were cured of HCV with DAA therapy [68]. Furthermore, the authors demonstrated excellent allograft function for HCV− recipients of HCV+ kidneys as well, with a median serum creatinine of 1.1 mg/dl at 6-month follow-up [68]. However, it should be noted that HCV+ to HCV− kidney transplantation is currently only performed under research protocols in the United States, as insurers will not reimburse or pay for prophylactic DAA therapy in HCV− patients.

Treatment

Vivanco et al. demonstrated that the utilization of induction therapy, including depleting agents (alemtuzumab or ATG) or IL2R, for HCV+ recipients was associated with improved patient and graft survival, compared with no induction treatment [69]. Sureshkumar et al. compared outcomes of HCV+ recipients using depleting and nondepleting regimens (basiliximab or daclizumab), and the authors found no difference in graft or patient survival, leading them to recommend selecting induction therapy independent of HCV serostatus [70]. However, another study demonstrated that fibrosis progression was faster among HCV+ transplant recipients receiving induction with daclizumab compared with depleting regimens [71]. As both HCV+ status and CNIs are associated with increased risk of post-transplant insulin resistance, one study assessed the role of converting from tacrolimus to cyclosporine A with the authors finding that HCV+ recipients may benefit from cyclosporine-based maintenance immunosuppression [72]. Maintenance immunosuppression also consists of steroids and MMF. Post-transplantation, HCV should then be treated with DAAs, which have excellent sustained viral response (SVR) and are safe and effective for kidney transplant recipients [66]. A recent Monte Carlo microsimulation by Shelton et al. demonstrated that among HCV+ recipients, liver fibrosis stage and access to HCV+ organs are important for determining optimal timing of kidney transplant and HCV treatment [73]. The authors found that for HCV+ kidney transplant candidates with further progression of liver disease (as evidenced by METAVIR (Meta-analysis of histological data in viral hepatitis) fibrosis score of F3), it was more cost-effective to treat HCV pretransplant, while for all other candidates, it was more cost-effective to pursue kidney transplantation with HCV+ organs followed by HCV treatment post-transplant [73].

Donors with Human Immunodeficiency Virus

Epidemiology

The utilization of HIV positive (HIV+) deceased donors for kidney transplantation began in South Africa in 2008, and over the course of a decade 43 kidney transplants from HIV+ donors were performed [74]. In the United States, 1.5% of patients with ESRD are HIV+, and among African Americans with ESRD the prevalence of HIV is even higher [75]. Despite this need, kidney transplantation from HIV+ donors was initially banned in the United States in 1988, but the HIV Organ Policy Equity (HOPE) Act, passed by US Congress in 2013 and implemented in 2015, now allows for transplantation of HIV+ kidneys into HIV+ recipients [76]. However, HIV+ to HIV− kidney transplantation in the United States can only be performed under research protocols.

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Diagnosis

In South Africa, HIV+ deceased donors have been used for kidney transplantation, and the diagnosis of HIV was confirmed by ELISA [77]. Some of the exclusionary criteria for these donors were severe sepsis, active tuberculosis, proteinuria, and elevated serum creatinine [77]. Because HIV serostatus of the deceased donors in South Africa as not known until time of death only two out of 43 donors were previously on antiretroviral therapy (ART) prior to donation [74]. The viral load for donors in South Africa varied from <960 to >150 000 [74]. However, characteristics of HIV+ donors who pose higher risk for recipients include history of drug resistance, detectable viral load (>200 copies/ml), X4 tropic virus, requirement of protease inhibitor therapy, history of virologic failure with ART therapy or no history of ART, and lower CD4+ count [78]. Similarly, candidate selection for HIV+ to HIV+ kidney transplantation is very important. In the multisite NIH study, as well as in South Africa, the criteria for recipients included viral load <50 copies/ml, CD4 count <200 cells/mm^2, stable ART regimen, and no active opportunistic infections [78].

Prognosis

Following HIV+ to HIV+ kidney transplantation, there have been concerns for infectious risks, particularly secondary to immunosuppression. However, reports utilizing kidneys from HIV-negative (HIV−) deceased donors to transplant HIV+ KT recipients have demonstrated that immunosuppression regimens necessary for transplantation can be safely administered in the setting of HIV given appropriate candidates selection [79–82]. Similarly, kidney transplantation for HIV+ recipients has been proven to provide a survival benefit compared with remaining on dialysis [83]. In their early experience of HIV+ to HIV+ kidney transplantation, Muller et al. reported two episodes of DGF among 27 recipients with 84% patient survival and 93% graft survival at 1 year post-transplant compared with 91% and 88% patient and graft survival among HIV− recipients, respectively [77].

Recurrence of HIV-associated nephropathy (HIVAN) was noted in 16% of recipients of HIV+ kidneys in South Africa [74]. However, another study, using HIV− organs, demonstrated HIVAN recurrence in nearly 70% of allograft biopsies despite undetectable viral loads at time of transplant [84]. The risk of HIVAN recurrence was thought to be related to the HIV viral reservoir residing within the kidney [85]. Additionally, there were concerns of HIV superinfection for HIV+ recipients of HIV+ organs due to a second viral strain being introduced, which could possibly become more resistant to ART treatment [74]. However, in the South African population, these potential risks have not been observed [74].

Treatment

Much of the research on immunosuppression regimens for HIV+ recipients has been based on transplantation of HIV+ recipients with HIV− kidneys, but the knowledge gained from this population may be used to influence decision making in the HIV+ to HIV+ kidney transplant population as well. Stock et al. did not initially use any induction treatment, and their maintenance immunosuppression consisted of MMF, steroids, and either cyclosporine or sirolimus [79]. In a subsequent study, Stock et al. found that the use of sirolimus for maintenance immunosuppression was associated with lower levels of HIV DNA, indicating a smaller reservoir size for these recipients [85]. Tan et al. used standard triple therapy for recipients of deceased donors with no induction therapy [86]. Others have used anti-CD25 for induction therapy [80–82, 87], while some studies have also used ATG for induction [88, 89]. Locke et al. found that HIV+ kidney transplant recipients who underwent induction therapy with ATG had 2.6-fold lower risk of acute rejection compared with their counterparts who had received no induction therapy [90]. The authors also demonstrated an increased risk for acute rejection associated with sirolimus-based maintenance immunosuppression regimens [90]. For HIV+ recipients of HIV+ organs, Muller et al. employed an immunosuppression regimen including ATG for induction, coupled with standard triple therapy [77]. Due to concerns of CNI toxicity when used in conjunction with protease inhibitors, protease inhibitor-based ART regimens are not optimal in the post-transplant setting [77]. Similarly, among HIV+ KT recipients of HIV− organs protease inhibitors should also be avoided if possible given associated increased risks of graft loss and mortality compared with other ART regimens [91].

Donation after Cardiac Death

Epidemiology

Although the majority of deceased donor kidneys are retrieved following brain death, the use of DCD donors has also been on the rise in several countries. As of 2013, in the United Kingdom, the Netherlands, and Belgium DCD donors accounted for 7.5–9 donors pmp (per million population) [92]. DCD donors now account for nearly 40% of all deceased donor kidney transplants in the UK [93]. In the United States, the number of DCD donors for kidney transplantation continues to increase as well, and as of 2017,

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nearly 3000 kidneys were transplanted from DCD donors, while fewer than 800 DCD kidneys were discarded [94]. In Japan, DCD donors account for 85% of deceased donor kidney transplants performed [6].

Diagnosis

There is some variation in the criteria to diagnose death for DCD donors internationally, but the overarching principles are the same [95]. Irreversible cardiopulmonary arrest must be confirmed, and irreversibility is defined as cardiac or respiratory function that cannot return spontaneously without medical intervention [95]. While in the United States and the UK there are no specific recommendations regarding medical personnel to confirm death (although the physician cannot be part of the retrieval team), in Canada two physicians are required and in Australia an intensivist is mandatory [95]. Likewise the observation period varies between 2 and 5 minutes, with the Institute of Medicine in the United States recommending 5 minutes [95]. In Australia, the retrieval team may reintubate the patient, but other measures such as mechanical ventilation and cardiac compressions cannot be pursued until after the organ procurement surgery has begun [95]. However, in other countries such as Canada, the United States, and the UK, such interventions are not permissible [95].

DCD donors are also divided into Maastricht categories (Table 57.4), according to the location and time of their death [96]. Controlled DCD donation refers to donors in categories III and IV, in which circulatory support is withdrawn in a planned setting, while categories I, II, and V refer to donors with unexpected, irreversible, cardiopulmonary arrest [13]. While some countries utilize controlled DCD donors (i.e. Australia, the UK, and the United States), in France and Spain uncontrolled DCD donors are more commonly used, and other countries such as the Netherlands support both controlled and uncontrolled DCD donors [93].

Table 57.4 Maastricht classification of donation after cardiac death [96].

Category	Description
I	Dead on arrival
II	Unsuccessful resuscitation
III	Anticipated cardiac arrest
IV	Cardiac arrest in a brain-dead donor
V	Unexpected arrest in an ICU patient

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Prognosis

The increased warm ischemia times for DCD kidneys have been thought to contribute to poor outcomes for DCD kidney transplant recipients. Soneijs et al. demonstrated that although DCD donors allowed for a substantial increase in the number of kidney transplants performed, they also carried a sevenfold increase in odds of primary nonfunction and 10-fold increased odds of DGF compared with recipients of DBD kidneys [97]. Other studies have shown that despite the increased risk of DGF, there is similar patient and graft survival for recipients of DCD kidneys compared with DBD donor recipients [92]. These results may be secondary to improved graft and patient survival following DGF for DCD kidney recipients compared with DBD transplant recipients who have experienced DGF [98]. Moreover, Wadei et al. also found similar kidney function between recipients of DCD and DBD donors [99]. Additionally, DCD kidneys from donors under the age of 50 years have been shown to have similar long-term graft function compared to SCD donors [100]. Furthermore, kidney transplantation from DCD donors has been proven to be more cost-effective than remaining on dialysis [101].

Because living kidney donation accounts for 80–85% of kidney transplantation in Japan, the utilization of deceased donor kidneys is limited [102]. However, of the deceased donors, many are Maastricht grade III or IV DCD donors, and of those many meet ECD criteria as well [102]. In this patient population, Tomita et al. described a graft survival of 74.8% at 5 years for DCD ECD kidneys compared with 95.6% for DCD SCD kidneys, although the difference was not statistically significant ($P = 0.102$, 102). In the UK, Nagaraja et al. found that DCD-ECD kidneys had equivalent short-term graft survival to DCD-SCD kidneys and DBD-ECD kidneys [103]. Likewise, the authors reported that increasing donor age was the only aspect of the ECD criteria that was significantly associated with decreased renal function in recipients of DCD kidneys [103].

Treatment

For recipients of DCD kidneys, ATG has been established as a cost-effective induction agent and was also associated with lower rates of DGF and acute rejection compared with IL2R therapy [104]. Mai et al. demonstrated that with the use of ATG followed by maintenance immunosuppression, including tacrolimus, MMF, and rapid steroid taper, yielded 3 years graft survival that was comparable to recipients of DBD kidneys [105]. Another study used a mammalian target of rapamycin inhibitor for uncontrolled DCD donors, and although there was no difference in graft function compared to CNI treatment, nearly 50% of the cohort was converted to CNI therapy [106] (Table 57.5).

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Table 57.5 Summary of findings: patient and graft survival for deceased donor kidney transplantation, stratified by deceased donor classification.

Deceased donor classification	No. of participants in study	Patient survival (follow-up time, months)	Graft survival (follow-up time, months)	Certainty of the evidence (GRADE)	Conclusion
Expanded criteria/ high KDPI donors	29 068	–	84.5% (12) 68.0 (36)	Low [18]	The use of expanded criteria/high KDPI donors is associated with acceptable patient and graft survival in selected recipients
	109 127	77%	93.7% (12) 66.4% (60)	Low [2]	
	170 668	–	66.9% (60)	Low [100]	
	244	97% (12) 86% (48)	89% (12) 70% (48)	Low [25]	
	298	98% (12) 95% (60)	95% (12) 83% (60)	Low [109]	
Infectious risk donors	622	97% (12) 91% (36) 84% (60)	93% (12) 83% (36) 84% (60)	Low [52]	IRD kidneys provide graft and patient survival similar to those of standard criteria donors
HCV+ donors	24	100% (6)	92% (6)	Low [63]	HCV+ donors provide acceptable opportunities for kidney transplantation
	6 250	66% (156)	57% (156)	Low [65]	
HIV+ donors	27	84% (12) 74% (60)	93% (12) 84% (60)	Low [77]	HIV+ donors provide acceptable opportunities for kidney transplantation
Donation after cardiac death	170 668	–	77.9% (60)	Low [100]	DCD kidneys offer acceptable short-term outcomes
	312	100% (12) 79% (60)	97% (12) 58% (60)	Low [99]	
	182	–	90% (36)	Low [105]	

DCD, donation after cardiac death; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IRD, infectious risk donor; KDPI, kidney donor profile index.

Conclusions

In summary, the utilization of deceased donor kidneys from ECD donors, those with high KDPI, DCD donors, and donors at risk for infectious diseases or with documented infections provide acceptable outcomes and improved patient survival compared with the alternative of remaining on dialysis. The decision to accept one of these organs should be preceded by an informative conversation between the recipient and members of the transplant team. Additionally, recipient selection for deceased donor kidney transplantation is very important. Bridging the gap between organ supply and demand may be partially achieved through the expansion of deceased donor kidney transplantation in the appropriate clinical setting in which recipients' risks and possible outcomes are clearly communicated.

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58

Early Medical and Surgical Complications After Kidney Transplantation

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- Kidney transplantation is the treatment of choice in patients with end-stage kidney disease (ESKD) because it confers a significant survival advantage compared to dialysis treatment [1, 2]. However, the survival remains poorer compared to the age-matched general population without ESKD [3]. Whilst there has been substantial improvement in the short- and intermediate-term allograft survival after kidney transplantation, there has been a lesser improvement in longer-term allograft survival, attributed to differences in etiology of short-term, compared to longer-term allograft failure. In this chapter, we will discuss the short-term medical and surgical complications that can potentially cause allograft failure within 1 year post kidney transplantation (Table 58.1), focusing on the practical approach, investigations, and treatment of these complications.
- Over the last two decades, the improvements in allograft and patient survivals after kidney transplantation have largely been attributed to the availability of more potent immunosuppressive agents (resulting in reduced incidence of acute rejection), improved stratification of immunological risk through the utilization of novel tissue typing technology (molecular human leukocyte antigen [HLA] typing and detection of donor-specific anti-HLA antibodies using Luminex technology), and better management of vascular risk factors prior to and after kidney transplantation [4–11]. Even though early mortality post-transplantation is relatively infrequent (5% at 1 year), the risk of mortality up to 6 months post-transplantation is three times higher compared to wait-listed patients on maintenance dialysis. Cardiovascular disease (CVD) and infections remain the two most common causes of early mortality post-transplantation, particularly among older patients, patients from socioeconomically deprived areas, and those with prevalent vascular disease or a long duration of ESKD [12, 13]. In addition, donor types and characteristics are likely to influence allograft and patient survival such that recipients of older live and deceased donor kidneys experience poorer allograft and patient survival compared to recipients of younger donor kidneys, with the magnitude of the survival differences more apparent in younger recipients [14, 15].
- The 1-year allograft survival in deceased and live donor kidney transplantation has improved substantially in the last decade. In Australia, primary allograft survival has increased from 80% to 94% between 1991–1992 and 2015–2016, respectively, for deceased donor transplants, and from 92% to 98% between 1991–1992 and 2015–2016, respectively, for live donor transplants [16, 17]. Similar trends have been observed in the United States (1-year allograft survival: deceased donor 87% in 1998 to 93% in 2014, live-donor 93% in 1998 to 97% in 2014) [18], Canada (1-year allograft survival: deceased donor 93% in 2007 to 94% in 2014, live-donor 96% in 2007 to 99% in 2014) [19], and the UK (1-year allograft survival: deceased donor 93% in 2005 to 94% in 2016, live-donor 95% in 2005 to 98% in 2016) [20, 21].
- Nonetheless, despite the improvement in short- and intermediate-term allograft survival, there has been little improvement in long-term allograft survival beyond 10 years post kidney transplantation, likely related to the lack of effective therapies for the common causes of late allograft failure including recurrent/de novo glomerulonephritis (GN), chronic antibody mediated rejections, and death with a functioning graft (particularly from CVD and cancer) [22, 23]. These trends have been observed in several countries, including Australia, Europe, and the United States [24–27].

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Table 58.1 Potential surgical and medical complications occurring in the first 12 months after kidney transplantation.

	0–3 months	>3–6 months	>6–12 months
Surgical complications			
Wound complications			
Renal vein/artery thrombosis			
Renal artery stenosis			
Ureteric (urine leak/obstruction/ischemia)			
Lymphocoele			
Medical complications			
Acute rejection/allograft failure			
Delayed graft function			
Disease recurrence			
BK viral infection/allograft nephropathy			

Grey, high likelihood of complications within the time frame after kidney transplantation; black, low likelihood of complications within the time frame after kidney transplantation.

Early Surgical Complications

Although our knowledge and understanding of the immune system has transformed the practice of renal transplantation since the first successful attempt in 1954, it is somewhat humbling to admit that our surgical techniques are still based on Alexis Carel's work at the very beginning of the twentieth century [28]. However, we have also refined those techniques to achieve 1-year allograft survival rates in excess of 97%, despite the perils of the immune system and ABO blood groups, not to mention the hurdles of morbid obesity, which has become the surgeons' greatest challenge in the twenty-first century [29].

Vascular Complications

Although the early pioneers attempted anastomoses in the forearm, a heterotopic position, such that the transplanted ureter can reach the bladder, was more logical. This has become standard practice, utilizing the recipient's iliac vessels. Usually the kidney is placed in an extraperitoneal pocket or space, which has the added advantage of both avoiding any risk of intraperitoneal adhesion formation and bowel obstruction, as well as avoiding any potential torsion of an intraperitoneal kidney, which can rotate around on its vascular pedicle, resulting in acute infarction [30]. This rare but catastrophic complication can occur if a kidney is placed within the peritoneal cavity, where immunosuppression reduces adhesion formation and bladder distension can push the lower pole up and lead to torsion. Nevertheless, this potential early complication remains possible, particularly in very thin recipients, and may explain why allograft failure secondary to technical complications is relatively more common in patients with a low body mass index (BMI) compared with those with higher BMI [31].

Even with the advent of minimally invasive laparoscopic kidney transplantation, early allograft failures secondary to torsion of a laparoscopically placed intraperitoneal kidney have been reported [32]. Consequently, refinement of the implantation technique by creating an extraperitoneal pocket postreperfusion, which "fixes" the kidney in place, has minimized this devastating early complication. Early allograft failures attributed to vascular mishaps are associated with significant morbidity, with the need for allograft nephrectomy as well as the risk of developing sensitization to exposed HLA-antigens.

Over the years, the availability of novel immunosuppressive agents such as the calcineurin-inhibitor (CNI) of tacrolimus has reduced the rates of early surgical complications, including a reduction in the incidence of renal vein thrombosis. Clinically, renal vein thrombosis would be heralded by dark-colored urine, followed by macroscopic hematuria and frequently accompanied by acute severe pain over the allograft as the capsule overlying the allograft stretches and subsequently ruptures. This vascular complication is now infrequent, but remains life-threatening in the early post-transplant period if unidentified. The risk factors for renal vein thrombosis are likely multifactorial, with vascular anatomy (of the allograft), surgical technique, and expertise likely contributing factors [33–36]. However, these findings have to be

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interpreted with caution as granular information such as the length of the renal vein, anastomosis site, or whether a caval extension was used in the setting of a right-sided deceased donor kidney were not available and may have modified the study findings. It is conceivable that venous thrombosis may occur because the length of the renal vein was left too long or indeed made even longer with the use of the attached inferior vena cava. Nevertheless, several registry-based observational studies have shown that recipients of kidney transplants using right-sided deceased donor or live donor kidneys were more likely to experience an increased risk of delayed graft function (DGF) and/or greater risk of early allograft failure attributed to surgical complications compared to left-sided donor kidneys [37]. While there is little doubt that right-sided kidneys pose a greater challenge to the surgical team, it is likely that a shorter renal vein combined with the longer renal artery on the right may contribute to the kinking of the vessels, resulting in the complication of renal vein thrombosis and premature allograft failure associated with the utilization of right-sided kidneys for transplantation. Smoking has also been shown to be a significant risk factor for renal vein thrombosis and therefore many transplanting centers have advocated that current smoking is considered an absolute contraindication to kidney transplantation [38].

These thoughts provide a convenient segue into complications from the arterial side of the renal allograft. Transplant renal artery stenosis is a well-recognized complication after kidney transplantation, with reported incidence varying between 1% and 25%. A recent cohort series of over 500 live donor kidney transplants reported an incidence of 3.8% for computer tomography (CT) angiography confirmed transplant renal artery stenosis, with total ischemic time and use of an arterial conduit identified as independent risk factors for this complication [39]. Transplant renal artery stenosis can be managed successfully with angioplasty and/or stent insertion, and rarely surgical exploration, but this complication has been associated with reduced 5-year allograft survival when compared with allografts without this complication.

Even though the direct visualization of renal vessels using digital subtraction angiography is considered the reference standard in detecting renal artery stenosis, less invasive techniques of Doppler ultrasound, CT angiography, and magnetic resonance (MR) angiography have largely superseded direct angiography in the screening for arterial stenosis [40].

Early allograft failure is usually deemed technical and assumed to be arterial or inflow in origin, rather than the rarely seen venous thrombosis. However, the details and cause of these early complications are often difficult to ascertain and are likely multifactorial in nature, with data from personal series and cohort studies adding little to the current understanding of the pathogenesis and subsequent prevention of allograft thrombosis [41].

Accelerated atherosclerosis and arterial calcification are highly prevalent in patients with ESKD, which are associated with significant morbidity and mortality. Widespread arterial disease is often considered a relative contraindication to kidney transplantation and therefore careful surgical evaluation by an experienced transplant surgeon is an essential aspect of determining surgical transplant suitability. In patients with or without arterial disease, dissection of the intima from the media of the recipient's iliac artery following arteriotomy during transplantation can lead to acute limb ischemia, in addition to the possibility of eliciting acute allograft thrombosis and failure [42]. Consequently, the careful selection of an appropriate anastomotic site avoiding calcified areas of atherosclerosis may mitigate this rare complication, but it can also occur in apparently healthy vessels. Dissection of the donor renal artery is an even less frequently reported complication that may be attributed to poor surgical technique or donor injury. If this is evident following reperfusion, urgent excision of the dissected segment where possible and re-anastomosis may lead to graft salvage, although successful angioplasty and surgical repair, as well as synthetic and autologous vein graft replacement have all been reported [43]. If left unrecognized, acute allograft ischemia will ensue, leading to early allograft failure.

Deceased donor kidneys usually have the added surgical advantage of an arterial patch which facilitates a wide arterial anastomosis, thereby reducing the risk of stenosis at the anastomotic site. However, the acute kinking of a long donor renal artery beyond the anastomotic site may occur, which may not become evident until after wound closure. For this reason, many transplanting units often advocate for early or immediate post-transplant Doppler ultrasound to assess renal vasculature, with patients returning immediately to theater for re-exploration if evidence is found of any compromised arterial flow within the allograft.

The appropriate positioning of the allograft within the extraperitoneal space following completion of vascular anastomoses is an important component of transplant surgery. The malposition of the allograft could lead to kinking or occlusion of the renal vasculature, but may also potentially cause torsion, resulting in acute vascular thrombosis and premature allograft failure. The authors advocate turning the allograft medially and, if necessary, creating a further extraperitoneal pocket beneath the rectus abdominis muscle such that the wound can be closed without compressing the allograft down on the recently created anastomoses. This medial placement may be more appropriate for thin recipients, as it requires only a simple technique

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modification and may avoid the intraperitoneal placement of the allograft that is often advocated for thin adult recipients.

A rare but potentially life-threatening complication is mycotic aneurysm, with an extremely low incidence reported in published series [44, 45]. The etiology of this complication is frequently attributed to *Candida species*, with the potential to cause catastrophic bleeding if unrecognized. The clinical team must have a high index of suspicion, particularly in patients presenting with acute abdominal pain and allograft dysfunction in an otherwise stable post-transplant setting. The primary goal of treating the mycotic aneurysm is excision of the infected aneurysm and re-establishing distal arterial flow. The management of a suspected ruptured mycotic aneurysm will focus on halting the hemorrhage, which will often require allograft nephrectomy as the infected arterial anastomosis ruptures into the extraperitoneal space. Ideally, all the allogeneic vasculature should be removed, with repair of the anastomotic site with autologous vein to patch the site or replacing a short segment of the infected iliac artery. Use of the recipient's own internal iliac artery, such that the mycotic segment can be excised and replaced, has been reported, but often these cases are undertaken under life-threatening circumstances, with covered synthetic stents placed within the external and common iliac artery to limit ongoing hemorrhage [46]. However, this approach may lead to an infected stent and in the context of an immunosuppressed patient now recently returned to dialysis following allograft removal may result in complicated infectious complications. If this occurs, the entire iliac arterial system can be replaced with deceased donor iliac artery such that an infected stent could be removed without losing the blood supply to the lower limb (unpublished observation), although an autologous long saphenous vein when available would be the preferred conduit. The management of the mycotic aneurysm has evolved from surgical reconstruction to an endovascular approach, the latter thought likely to be associated with lower risk of morbidity and immediate mortality. Even though there is no high-level evidence comparing the efficacy and safety of open surgery versus endovascular stenting in this rare and unique setting, it does allow clinicians to select the most appropriate approach depending on the acuteness of the presentation, clinical circumstances, and expertise of the treating surgical teams.

Over the last decade, there is a greater focus on the timing of the surgery, particularly the time taken for vascular anastomoses (i.e. warm ischemic time) as well as preservation of the allografts using cold or normothermic perfusion machines [47]. Data from the United Network of Organ Sharing (UNOS) and Eurotransplant registries have shown an inverse association between warm ischemic time and allograft survival independent of cold ischemic time, such that for every 10 minutes increase in warm ischemic time, there was up to an 8% increased risk of allograft failure [48]. A smaller cohort study, also from Eurotransplant, similarly showed a direct relationship between warm ischemic time and risk of DGF and allograft fibrosis, independent of the duration of cold ischemic time [49]. Despite the recognition that shorter warm ischemic time is associated with better allograft outcome, it is somewhat surprising that almost 30% of the kidney transplants in these studies have reported times of over 45 minutes, reinforcing the need for careful speed under stressful circumstances. With the evolution of laparoscopic and more recently robotic kidney transplantation techniques, it will become ever more important to protect the kidney from prolonged warm ischemic injury, highlighting the critical role in the learning curve of the surgeon [50].

Ureteric Complications

The incidence of ureteric complications after kidney transplantation is estimated at between 2% and 12%, predominantly related to urine leak and obstruction [51]. The role of intra-operative ureteric stenting (versus no stenting) remains a subject of debate among transplant surgeons and urologists. One of the largest published randomized controlled trials (RCTs) of 300 kidney transplant recipients showed that these major urological complications could be completely avoided in the early transplant period with stent usage [52]. A systematic review of seven studies showed that routine prophylactic stenting of the ureter significantly reduced the risk of major urological complications, at the expense of an increased risk of urinary tract infection, unless prophylactic cotrimoxazole was prescribed [53]. In addition, there is a suggestion that ureteric stents may increase the risk of developing BK viral allograft nephropathy (BKVAN), although a definitive causal relationship has not been established [54]. Given these findings, the majority of the transplanting units have advocated for the routine prophylactic placement of ureteric stent to reduce the risk of early urine leak or obstruction. Nevertheless, ureteric stent avoidance does not necessarily result in greater rates of urological complications, with several authors advocating selective stent usage to avoid the increased risk of urinary tract infection [55]. Meticulous surgical technique remains an important facet of reducing the risk of post-transplant urological complications.

There is considerable interest among transplant urologists regarding the optimal timing of ureteric stent removal post-transplant. Several small randomized controlled trials have shown early stent removal to be beneficial. A recent

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systematic review of five studies comprising 1127 kidney transplant recipients has shown that early stent removal within the first 2 weeks significantly reduced the incidence of urinary tract infection, provided the stent was not sutured to the urinary catheter [56]. However, the quality of evidence supporting these findings is poor. Consequently, there is substantial variation in the timing of ureteric stent removal between transplanting sites, which may also depend on several nontransplant-related factors such as theater availability and expertise in cystoscopy.

Urine leak in the early post-transplant period is often difficult to diagnose, but may be suspected when there is an unexpected worsening of allograft function in the setting of a new perinephric collection. This can be confirmed by a high creatinine concentration in the drain fluid when compared with serum creatinine concentration. There are several risk factors for urine leak, including ureteric stent migration out through the renal hilum, urine leak post biopsy, or leak from an infarcted area of kidney cortex, although prolonged surgical procedure beyond 3 hours has also been identified as a risk factor. Management of confirmed urine leak in the early post-transplant period is often surgical re-exploration even though anastomotic dehiscence is unusual, particularly if the ureteric stent and urinary catheter remains in situ. However, percutaneous drainage may have a role, particularly if the volume of urine leak is small and providing infection can be avoided. If a urine leak has occurred later post-transplant, conservative treatment with bladder decompression by prolonged catheterization and management of the contributing factors may be sufficient to ensure spontaneous resolution of these leaks without surgical intervention [57].

Ureteric obstruction is an infrequent occurrence in the era of routine placement of ureteric stents. Nevertheless, ureteric stenosis or obstruction may occur following routine removal of the stent and therefore must be excluded in situations where there is an acute deterioration of allograft function following stent removal. A dedicated ultrasound assessment is the initial imaging modality of choice and is usually sufficient to exclude ureteric obstruction. Management of ureteric obstruction does depend on the cause of the obstruction and local expertise, but often involves an antegrade percutaneous nephrostomy and subsequent stent insertion, unless the ureteric anastomosis can be accessed satisfactorily via cystoscopy. Many urologists advocate placement of the ureteric anastomosis at the lowest possible part of the bladder wall, rather than on the much more accessible bladder dome. However, the former is rarely practical in patients with a long history of anuria with a shrunken bladder.

Ureteric infarction can occur when the blood supply to the transplanted ureter is compromised, often in the setting of a ligated or thrombosed lower polar artery. The only available salvage treatment option is surgical ureteric reconstruction by anastomosing the renal pelvis of the allograft to the ipsilateral native ureter, which if successful can offer reasonable long-term allograft outcome. However, more distal strictures can be managed by raising a Boari flap from the bladder, as has been reported in 14 patients from a cohort study [58].

Lymphocele

Lymphocele formation occurs in approximately 4% of kidney transplant recipients [59] and, if of sufficient size, may lead to compression of the vasculature and/or transplant ureter causing acute or subacute allograft dysfunction and venous obstruction. Multiple risk factors for lymphcoele development have been reported, including the use of mammalian target of rapamycin (mTOR) inhibitors, although causal relationships have not been clearly established [60]. There is currently no consensus regarding the optimal management of lymphoceles, and it is likely to depend on the size, unit protocol, the pressure effect on surrounding structures, and the degree of allograft dysfunction attributed to the lymphocele. In a systematic review of 52 studies evaluating the different treatment strategies for post-transplant lymphocoeles, percutaneous drainage was reported to be effective in 25% of cases and is often considered the first-line treatment option in most transplanting units. The alternative option, particularly following failure of percutaneous drainage, is laparoscopic or open surgical drainage; the latter may be preferred for inferiorly placed lymphocele (and therefore difficult to identify the ureter) given the potential risk of ureteric injury [59].

Wound Complications

The incidence of wound complications such as wound dehiscence and infection following kidney transplantation may be up to 25%, particularly in high-risk groups with morbid obesity and low functional status [61]. This complication often leads to prolonged hospitalization or readmissions, requiring additional nursing/wound care, adjustment of immunosuppression, and excess healthcare resource utilization.

In a single institution study of over 2200 kidney transplant recipients, the incidence of incisional hernia formation was 5% at 5 years, increasing to 7% at 10 years. Both recipient obesity and surgical site infection were risk factors for subsequent hernia formation in this large series, with surgical site infection associated with almost a 30 times the risk of developing incisional hernia [62]. Patients

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should be adequately informed of these potential complications prior to transplantation, although informed consent should not abrogate the need for careful aseptic technique and tissue handling to minimize such wound complications.

Conclusion

There is an evolution of minimally invasive surgical techniques for kidney transplantation, including the creation of anastomoses using laparoscopic and now robotic-assisted surgery but the long-term allograft outcomes of these approaches remain unknown. The challenge for transplant surgeons going forward is how to minimize the effects of the learning curve associated with these new minimally invasive techniques in morbidly obese recipients, particularly when slow anastomoses increases the risk of DGF and jeopardizes long-term allograft survival. Perhaps one of the greatest challenges is the transplantation of an allograft with multiple arteries and veins, as well as a bifid ureter, which will always challenge the experienced surgical team to minimize early surgical complications.

Early Medical Complications

Acute Rejection

Acute rejection of the kidney allografts following transplantation continues to be a major impediment to long-term allograft survival [63]. Even though the incidence of early acute rejection has decreased substantially over the last few decades with the introduction of more potent induction and maintenance immunosuppression (resulting in improvement of short- and intermediate-term allograft survivals), the incidence of acute rejections within the first 12 months post-transplantation is reported to be between 8% and 20% in most countries, with one in five allograft failures within the first year post-transplant attributed to acute rejection [17, 18, 64]. Compared to kidney transplant recipients who have not experienced acute rejection, recipients who have experienced cellular rejection have over a 1.5-fold greater risk of allograft failure, with those experiencing more severe rejections such as antibody-mediated rejections and/or vascular rejection associated with the poorest prognosis [63, 65, 66]. The most effective treatment strategies (combination of treatments and dosing of treatments) for cellular and antibody-mediated rejections remain uncertain, although interventions to eliminate circulating T cells (e.g. antithymocyte and antilymphocyte antibodies, alemtuzumab) and/or remove circulating donor-specific anti-HLA antibodies (plasmapheresis, intravenous immunoglobulin, anti-B cell, and anti-plasma cell therapies) are often required in the treatment of steroid-resistant cellular/vascular rejections and antibody-mediated rejections, respectively [67–72].

The risk of hyperacute rejection has largely disappeared with the evolution of novel immunological assays to detect for the presence of pretransplant donor-specific anti-HLA antibodies including luminex assays and flow cytometric cross-matching technique, which has facilitated a more accurate assessment of pretransplant immunological risk and appropriate selection of immunologically compatible donor kidneys. Even though pretransplant donor-specific anti-HLA antibodies are known to be associated with poorer outcome, including a 40 times greater risk of antibody-mediated rejection and premature allograft failure [73], the recognized limitations of the Luminex assays combined with the uncertainty regarding the differential adverse impact of the type, quantity, and quality of the donor-specific anti-HLA antibodies have led to a cautious but varying approach to the interpretation of these assays [7]. Consequently, there continues to be considerable debate regarding the acceptance (and nonacceptance) of donor kidneys for transplantation in patients with pre-existing donor-specific anti-HLA antibodies. There is an increasing number of non-HLA alloantibodies targeting vascular and angiotensin receptors or proteins expressed on endothelial cells (e.g. anti-endothelin-1 type A receptor antibody, antivimentin antibody, anti-angiotensin II type 1 receptor antibody) that are recognized to influence the development of antibody-mediated rejection and allograft failure [74–77], but the additional clinical significance of these non-HLA antibodies beyond the routine detection of donor-specific anti-HLA antibodies, combined with the cost of these assays, has preclude the inclusion of non-HLA antibodies in the standard immunological risk assessment for potential kidney transplant candidates.

Desensitization techniques designed to deplete anti-A or -B and donor-specific anti-HLA allo-antibodies prior to kidney transplantation have facilitated successful transplantation across the ABO barrier and in patients with pretransplant donor-specific anti-HLA antibodies, respectively. Even though the outcomes of ABO-incompatible kidney transplantation were similar or slightly reduced compared to ABO-compatible transplants [78, 79], the optimal desensitizing regimen remains unclear but typically comprises interventions aimed to remove circulating anti-A or -B antibodies and treatment strategies to suppress antibody production by B cells/plasma cells. A systematic review of 83 cohort, case-controls/reports, and registry studies comprising 4810 ABO-incompatible recipients showed that allograft and patient survivals exceeded 90%, with low-

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level evidence suggesting that preconditioning therapies consisting of immunoadsorptive therapy and rituximab may be associated with better allograft outcomes [80]. The risk of acute rejection after ABO-incompatible kidney transplantation varies between studies (3–52%), with the majority of rejections attributed to antibody-mediated rejections [80] and likely related to pre- and post-transplant anti-A/B titers such that patients with high levels of anti--A/B titers prior to transplantation or who experienced a rapid rebound in anti-A/B titers post-transplant were more likely to experience antibody-mediated rejections. Nevertheless, these associations remained inconsistent, possibly related to differences in desensitization regimens/intensity of immunosuppressive agents, differences in the absolute levels of anti-A/B titers pretransplant, differences in measurement assays of anti-A/B titers, and the possibility of utilizing A2 donor kidney for blood group O or B patients [81–85]. Even though death-censored allograft survival following ABO-incompatible kidney transplantation is similar to that of ABO-compatible kidney transplantation, these recipients may have a greater risk of mortality at 1-year post-transplant, attributable to infectious complications presumably related to the greater burden of immunosuppression from desensitization treatments [86].

There is a general reluctance among clinicians to consider transplantation across the ABO barrier and pretransplant donor-specific anti-HLA antibodies because of the perceived incremental risk of adverse allograft outcome, but the impact on allograft outcome may be similar to transplants with pretransplant donor-specific anti-HLA antibody [87]. A recent cohort study of 681 live donor kidney transplant recipients showed that ABO-incompatible kidney transplant may reduce the likelihood of developing de novo donor-specific anti-HLA antibodies, independent of the use of rituximab, but the exact mechanism of this favorable effect remains unknown and conflicting [88].

Highly sensitized patients often experience prolonged waiting time, lower transplantation rate, and a greater risk of mortality and adverse allograft outcomes following transplantation [89]. Desensitization strategies to remove circulating donor-specific anti-HLA antibodies have resulted in successful live-donor kidney transplantation in HLA-sensitized patients, with patient survival superior compared to dialysis treatment and waiting for a compatible donor kidney [90]. However, the longer-term outcome of cross-match positive kidney transplant recipients remains inferior compared that for to cross-match negative recipients [91]. The optimal desensitization regimen in cross-match positive HLA-sensitized live donor kidney transplant remains unknown, but typically comprises plasmapheresis, intravenous immunoglobulin and/or anti-B cell therapy/splenectomy [90, 92]. Similar regimens have also enabled the successful transplantation of these sensitized patients, with significant reduction in waiting time on the deceased donor transplant wait-list [93, 94]. A recent study of 25 highly sensitized patients showed that an endopeptidase, IgG-degrading enzyme derived from *Streptococcus pyogenes* (IdeS), substantially reduced donor-specific anti-HLA antibodies therefore allowing HLA-incompatible transplantation in 96% of these patients [95]. Even though this therapy appears promising, longer-term prospective trials including larger numbers of patients are required for better appraisal of this molecule.

The availability of high-resolution molecular HLA-typing methods has allowed for a more accurate assessment of HLA compatibility at the structural (or epitope) level, which has revolutionized our understanding of immunological compatibility in kidney transplantation. The importance of epitope matching has been highlighted in multiple cohort studies such that incremental mismatched epitope load is associated with a greater risk of acute rejection and poorer longer-term allograft outcome [8, 96–100]. Consequently, several countries have implemented allocation programs designed to preferentially allocate donor kidneys with a lower number of donor/patient epitope mismatched load, which may ultimately reduce the long-term risk of acute and chronic antibody-mediated rejection and improve long-term allograft survival [101, 102].

Over the last two decades there have been several clinical trials designed to examine the efficacy of different induction and maintenance immunosuppressive regimens. Even though the optimal induction regimen remains debatable, it is widely accepted that an immunosuppressive regimen comprising of tacrolimus and mycophenolate is the preferred maintenance immunosuppressive regimen, with other novel immunosuppressive agents inferior to or at most comparable to the efficacy of this regimen. Table 58.2 summarizes the important multicenter clinical trials comparing the efficacy of different de novo induction and maintenance immunosuppressive regimens on short-term allograft outcomes after kidney transplantation (only RCTs of more than 150 randomized patients since 2005 are shown).

Delayed Graft Function

DGF is a common complication after kidney transplantation (20–50%), with the highest incidence observed after donation after circulatory death (DCD) kidney transplants [116]. DGF is a pathophysiological process of ischemia-reperfusion injury following organ procurement, leading to excess inflammatory response, including indirect activation of the innate and adaptive immunity [117].

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Table 58.2 Summary of the randomized controlled trials comparing the short-term efficacy of different immunosuppressive regimens in de novo kidney transplant recipients.

Trial	Design	*N*	Primary endpoint	Outcome	Adverse events
Induction therapy randomized controlled trials					
Brennan et al. [103]	RCT, superiority study of basiliximab vs. antithymocyte globulin	278	Composite of acute rejection, delayed graft function, graft loss, and death at 12 months	Composite endpoint: basiliximab 56% vs. antithymocyte globulin 50% ($P = 0.34$) Less BPAR in antithymocyte globulin group	Similar
Thomusch et al. [104]	RCT, superiority study Basiliximab + Tac/MMF ± P withdrawal day +8 vs. rATG + Tac/MMF/P + withdrawal P day +8	615	BPAR 12 months	BPAR rates similar: basiliximab (11% with or without P withdrawal) vs. rATG (10%)	Less PTDM (post-transplant diabetes mellitus) in steroid withdrawal groups
3C Study Collaborative Group [105]	RCT, superiority study of alemtuzumab vs. basiliximab	852	BPAR at 6 months	BPAR: alemtuzumab 7% vs. basiliximab 16% ($P < 0.01$)	More BK infection with alemtuzumab
Maintenance therapy randomized controlled trials					
Ekberg et al. (ELITE-Symphony study) [106]	RCT, superiority study of four regimens: (i) standard-dose CsA + MMF + P, daclizumab induction with MMF + P, (ii) low-dose tacrolimus, (iii) low-dose CsA, and (iv) low-dose sirolimus	1645	eGFR at 12 months	eGFR higher in low-dose tacrolimus vs. all other groups ($P < 0.01$) 6 months BPAR/12 months allograft survival: low-dose tacrolimus 11%/96%, low-dose CsA 22%/94%, low-dose sirolimus 35%/92%, standard-dose CsA 24%/92%	SAE more common in low-dose sirolimus group, incidence PTDM (post-transplant diabetes mellitus) higher in low-dose tacrolimus group (8%)
Vincenti et al. (BENEFIT study) [107]	RCT (phase 3), noninferiority study of MMF + P with (i) low-intensity (LI) belatacept, (ii) more intensive (MI) belatacept, and (iii) CsA	686	Three endpoints: 12 months composite graft and patient survival, composite renal impairment, and BPAR	Compared to CsA, belatacept was noninferior for graft/patient survival, superior in 12 months renal function, noninferior in BPAR (except MI belatacept was inferior)	Similar, more cases of PTLD (particularly brain) in belatacept groups
Durrbach et al. (BENEFIT-EXT study) [108]	RCT (phase 3) in expanded criteria donor kidney transplants, noninferiority/superiority study of LI and MI belatacept vs. CsA	578	12 months composite graft and patient survival (noninferiority), composite renal impairment (superiority)	Compared to CsA, belatacept was noninferior for graft/patient survival, superior in 12 months renal function BPAR similar	Similar, more cases of PTLD in belatacept groups
Russ et al. [109]	RCT (phase 2), noninferiority study of three doses of sotrastaurin + standard/reduced-dose tacrolimus + P vs. standard-dose tacrolimus + MPA + P	298	6 months composite of BPAR, graft loss, death or lost to follow-up	Similar outcomes (sotrastaurin 100 mg group discontinued because of high event rate) Median eGFR similar	Similar, but more gastrointestinal events and transient increase in heart rate in sotrastaurin groups

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Tedesco-Silva et al [110]	RCT (phase 2), noninferiority study of CsA + everolimus vs. sotrastaurin + everolimus (stage 1 efficacy study), then dose-finding study for sotrastaurin (stage 2)	311 (both stages)	Composite of BPAR, graft loss, death or lost to follow-up	Stage 1: composite efficacy failures at 3 months similar, higher in sotrastaurin group at 12 months (17% vs. 11%) Stage 2: composite efficacy failures higher in sotrastaurin groups (27–35%) vs. CsA group (19%) at 12 months	Similar, but more gastrointestinal events and transient increase in heart rate in sotrastaurin groups
Lebranchu et al (Concept study) [111]	RCT, superiority study of CsA + MMF + P, randomized at week 12 to continue CsA or change to sirolimus P stopped month 8	193	52 weeks adjusted CrCl	Mean (95%CI) CrCl: sirolimus 68.9 (65.9, 71.8) vs. CsA 64.4 (61.7, 67.1) ml/min/1.73 m^2; $P = 0.02$ Numerically more BPAR in sirolimus group	More adverse events in sirolimus group (aphthous stomatitis, diarrhea and acne)
Weir et al. (Spare-the-Nephron trial) [112]	RCT, superiority study of MMF + CNI, randomized days 30–180 post-transplant to MMF + CNI vs. MMF + sirolimus	299	Mean % change in measured renal function from baseline to 12 months	Mean % change greater in MMF + sirolimus group vs. MMF + CNI group at 12 months (24% vs. 5%, $P = 0.01$) Not significant between groups at 24 months	Similar in both groups, numerically higher rate of discontinuation MMF + sirolimus group
Tedesco Silva Jr. et al. (A2309 study) [113]	RCT, noninferiority study of everolimus + reduced exposure CsA vs. standard-exposure CsA + MPA	833	12 months composite of BPAR, graft loss, death or lost to follow-up	12 months efficacy failure rates were noninferior in the everolimus 1.5 mg (25%) and 3.0 mg (22%) vs. MPA (24%) groups Similar eGFR	Higher discontinuation in the everolimus groups
Flechner et al. (Orion study) [114]	RCT, superiority study of sirolimus + tacrolimus elimination + P, sirolimus + MMF + P vs. tacrolimus + MMF + P	469	12 months eGFR	Similar eGFR at 12 months Group 2 discontinued due to high rate of BPAR Similar rate of BPAR in remaining two groups	Higher rate of discontinuation in sirolimus + tacrolimus elimination group (34%) vs. tacrolimus + MMF (22%)
Pascual et al (TRANSFORM study) [115]	RCT, noninferiority of everolimus + reduced exposure CNI + P vs. standard-exposure CNI + MPA + P	2037	12 months composite of BPAR or eGFR <50 ml/min/1.73 m^2	Similar outcomes De novo DSA and antibody-mediated rejections similar	Fewer BK virus and CMV infections but greater discontinuation rate in everolimus group compared to standard CNI group

BPAR, biopsy-proven acute rejection; CMV, cytomegalovirus; CNI, calcineurin-inhibitor; CrCl, creatinine clearance; CsA, cyclosporine; eGFR, estimated glomerular filtration rate; MMF, mycophenolate mofetil; MPA, mycophenolic acid; P, prednisolone; PTLD, post-transplant lymphoproliferative disease; rATG, rabbit antithymocyte globulin; RCT, randomized controlled trials; SAE - serious adverse event;ATG - anti-thymocyte globulin;PTDM = post-transplant diabetes mellitu;SAE - serious adverse event; DSA = donor-specific anti-HLA antibody

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In the ensuing ischemic injury, there is osmotic injury to cells in addition to an accumulation of reactive oxygen species [118, 119], the damage of which can be reduced with appropriate preservation fluids, optimal storage conditions, and adequate intra- and post-operative fluid balance [120–122]. After reperfusion, the combination of vasoconstriction, activation, and recruitment of innate and adaptive immune cells contributes to sustained epithelial cell damage and inflammatory response, manifesting clinically as DGF [116, 123]. In a prospective longitudinal study of 318 kidney transplant recipients, kidneys that were complicated by DGF showed significantly higher degrees of tubulo-interstitial inflammation (i.e. higher Banff *t* and *i* scores) and higher Banff cumulative chronicity scores in protocol biopsy at 3 months compared to kidneys without DGF, suggesting a potential role of inflammation in determining the longer-term allograft outcomes in recipients with DGF [124].

The clinical manifestations of DGF vary in severity, with definitions of DGF ranging from an asymptomatic slowing in the improvement of allograft function to sustained oligoanuria and hyperkaliemia resulting in the need for dialytic support. The optimal definition for DGF remains unknown and there is no single definition of DGF that has been shown to be superior in predicting the risk of adverse allograft outcome after kidney transplantation. Even though the requirement of dialysis within the first week of transplant remains the most preferred and accepted definition of DGF [125, 126], there is likely to be a dose-dependent effect between DGF duration and allograft failure, with DGF duration of beyond 7 days consistently associated with the highest risk of allograft failure [127–129].

Risk factors associated with ischemia reperfusion or excess inflammatory response such as prolonged ischemic time, older donors and recipients, higher recipient BMI, and longer dialysis duration have been shown to increase the probability of DGF [130, 131]. The consequences of DGF are substantial, with short- and long-term adverse outcomes leading to prolonged hospitalization and excess utilization of healthcare resources [132]. Even though the association between DGF and adverse longer-term allograft survival is well established, there continues to be uncertainty as to whether this association remains consistent in both donation after brain death (DBD) and DCD kidney transplantation. One of the main limitations when interpreting the study findings regarding the "true" incidence of DGF and the association between DGF and allograft outcomes is the significant heterogeneity in the definition of DGF, which is present even after adjustment for patient- and center-level characteristics, and therefore caution must be exercised when interpreting these findings or when considering the most appropriate definition of DGF for clinical trials [133]. In a meta-analysis of 33 studies totaling 151 594 kidney transplant recipients, DGF was associated with over 40% greater risk of allograft failure and poorer allograft function, with the majority of these studies confined to DBD kidney transplant recipients [134]. However, the association between DGF and allograft outcome in DCD kidney transplants remains indeterminate, with several cohort studies showing a lack of association between DGF and allograft survival [135, 136]. This observation is thought to be related to a differential susceptibility between DBD and DCD kidneys to the deleterious effects of cold ischemic injury, such that brain death induces a greater upregulation of inflammatory gene expression profile in the DBD kidneys compared to DCD kidneys, which may to some extent explain why DGF in DCD kidneys may not have the same deleterious effects on allograft survival as DBD kidneys [137]. However, a paired-kidney registry analysis from Australia and New Zealand showed that recipients of DCD kidneys with DGF experienced a fourfold increased risk of allograft failure at 3 years post-transplant compared with those without DGF, suggesting that the deleterious effect of DGF in DBD transplants may also be extended to recipients of DCD kidneys [138].

Several population cohort studies have shown that DGF may predispose to an increased risk of acute rejection, possibly related to reduction in immunosuppression and the excess immunological reactivity resulting from an indirect activation of the innate and adaptive immune responses [116, 139, 140]. There is, however, uncertainty as to whether the adverse association between DGF and allograft outcome is related to the presence of acute rejection or the presence of "susceptible" donor types but it does suggest the need for careful monitoring and evaluation for acute rejection in recipients who have experienced DGF [129, 141, 142].

The presence of DGF increases the complexity in post-transplant management, with clinicians requiring to differentiate DGF from other acute pathology, particularly early acute rejection, which requires an increase in the intensity of immunosuppression, compared to the judicious reduction in CNI (which causes vasoconstriction and may exacerbate DGF) in the presence of DGF. The practical approach to DGF is to determine whether dialysis is clinically indicated after exclusion of competing pre- and postrenal complications and early consideration for allograft biopsy to discern acute tubular necrosis (suggesting DGF) from acute rejection. Repeated imaging of the allograft vasculature and frequent biopsies may be necessary in the presence of prolonged DGF. There is little data to guide the management of prolonged DGF in the absence of acute rejection. Other than avoiding nephrotoxins, pre-emptive

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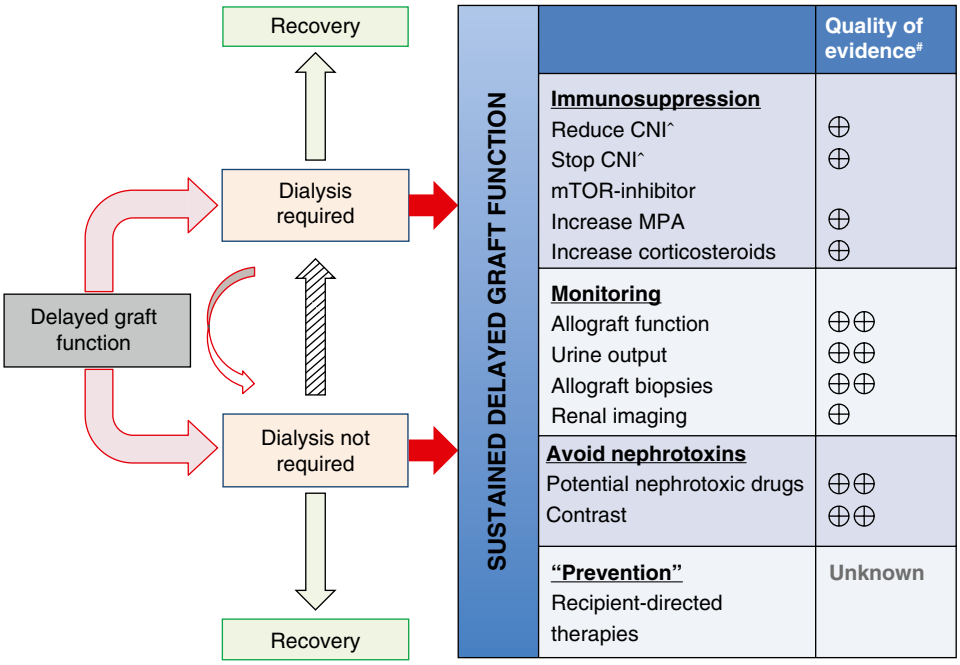
delaying the introduction of CNI (where there is a high pretransplant probability of DGF) and substituting CNI for mTOR-inhibitors or antilymphocyte therapy are unproven strategies, although the latter approach may be practical in the concurrent presence of acute rejection or in highly sensitized recipients at high risk of acute rejection [143–147]. Figure 58.1 shows a practical algorithm in the management of recipients with DGF. Given the greater understanding of the risk factors and complexity of the pathophysiological mechanisms contributing to the development of DGF, there have been multiple clinical trials utilizing promising therapies (e.g. belatacept, toll-like receptor monoclonal antibody, pegylated carboxyhemoglobin bovine) that may lead to a reduction in the burden of DGF and consequently improve longer-term allograft outcome. In addition, normothermic machine perfusion has been shown to effectively assess and potentially ameliorate the ischemia reperfusion injury prior to implantation [148]. A large multicenter RCT comparing the efficacy of normothermic perfusion with standard cold storage is currently underway in the UK which may help in defining the role of this technology in the future [149].

Early Disease Recurrence

Primary glomerulonephritis (GN) is one of the leading causes of ESKD worldwide [150–152]. In Australia and New Zealand, primary GN accounts for 20% of incident ESKD and is the most common indication for kidney transplantation (ANZDATA registry 2017 report). In the United States, Canada, and the UK, ESKD attributed to primary GN contributes to between 10% and 20% of overall burden of ESKD. All GN subtypes can potentially recur after transplantation, with the prevalence of GN recurrence between 3% and 15%, although patients with IgA nephropathy, membranoproliferative GN (MPGN), focal segmental glomerulosclerosis (FSGS), and idiopathic membranous nephropathy (IMN) are more likely to experience disease recurrence compared to other GN subtypes, including those with presumed or advanced GN without a clear histological diagnosis [152]. Even though the risk of GN recurrence is directly proportional to time post-transplant, early GN recurrence resulting in allograft failure within 12 months is more common in patients with FSGS and MPGN. Up to 30% of patients with FSGS experience disease recurrence post-transplant [152–155], particularly those with primary FSGS whereby the presence of a circulating glomerular permeability factor might directly induce podocyte damage and early recurrence [156]. In contrast, patients with familial FSGS have low risk of disease recurrence, with the belief that the intrinsic genetic defect of the host kidney is corrected by receiving a donor kidney without this defect [157]. The treatment of recurrent FSGS remains largely unproven, with plasmapheresis, immu-



#Quality of evidence based on retrospective case/cohort studies, recommendations and personal opinions. ⊕ low-quality, ⊕⊕ moderate quality.^denotes the possibility of concurrent introduction of T cell depleting antibody

Figure 58.1 Management algorithm of the practical approach to delayed graft function in kidney transplant recipients.

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noadsorption, and alternative immunosuppressant (e.g. cyclophosphamide, abatacept) used with varying successes, but the optimal treatment strategy remains unknown [158–161].

Disease recurrence from primary MPGN is relatively common, with high rates of recurrence (up to 100%) and allograft failure (50%) observed for those with type I and II MPGN (majority were reclassified as immune complex-mediated GN according to the new classification [162]) and over 50% of recurrence occurring within 12 months post-transplant [152, 163–165]. Similar to FSGS, the optimal treatment for recurrent disease is not established, limited to case reports of successful treatment with the use of plasmapheresis and other immunosuppressants, including cyclophosphamide, eculizumab, and rituximab [166–169]. Although the recurrence rate of IgA nephropathy and IMN may be up to 50% post-transplant, early recurrence is unusual and the progression of disease recurrence to allograft failure is typically slow [170]. It is likely that the incidence of GN recurrence or allograft failure attributed to GN recurrence may be underestimated because of the likelihood of selection bias (i.e. systematic differences in the selection and listing of ESKD patients with different GN subtypes), misclassification and indication bias (where kidney biopsy may be carried out only for specific clinical indication and therefore may fail to identify asymptomatic incidental cases of disease recurrence) and the competing risk of other causes of allograft failures.

Patients with systemic diseases and ESKD resulting from secondary GN (such as atypical hemolytic uremic syndrome [aHUS], systemic lupus erythematosus [SLE], anti-glomerular basement membrane [GBM] disease, and crescentic GN [e.g. from systemic vasculitis]) may experience GN recurrence after kidney transplantation but these relapses are often late and infrequently lead to allograft failure [170]. In patients with antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, the relapse rate (often at nonrenal systems) has been reported to be 0.02 per patient-year, with no consistent association found between ANCA subtypes or disease severity pretransplantation and risk of relapse [171–173]. The incidence and outcome of patients with recurrent lupus nephritis post-kidney transplantation are unclear, with the majority of the reports from single-center and registry studies. The reported incidence of recurrent lupus nephritis varies between 0% and 44% [174], with patients who had experienced recurrent lupus nephritis at a greater risk of allograft failure and mortality [175–178]. However, this association remains inconsistent [179]. In patients with anti-GBM disease, disease recurrence after kidney transplant is less than 5% in the era of modern immunosuppression, and allograft failure from disease recurrence is exceedingly rare [180, 181]. Prior to the availability of the C5-inhibitor eculizumab (Soliris®), the risk of disease recurrence following transplantation of patients with aHUS was up to 80%, and a substantial proportion of patients would lose their allograft from recurrent disease within the first year post-transplant, therefore kidney transplantation is considered a contraindication for patients with aHUS [182]. With prophylactic use of eculizumab, kidney transplantation appears safe and associated with excellent allograft outcome, even in those with pathogenic mutations known to be associated with a high risk of disease recurrence [183–185]. There have been reports of successful live donor kidney transplantation without the use of prophylactic eculizumab but this is generally not recommended or undertaken with extreme caution in patients with certain genetic mutations (e.g. membrane-associated complement regulator membrane cofactor protein mutation) and frequent monitoring [186, 187].

Table 58.3 shows the primary causes of ESKD that are known to recur post-transplant, stratified by the timing of disease recurrence and available treatment options.

BK Viral Infections

BK viral infection is common after kidney transplantation, and early recognition and treatment can prevent progression to allograft failure from BKVAN [188]. Because cellular adaptive antiviral immunity is critical in the control of BK viral infection and BKVAN, the overall intensity and cumulative exposure to chronic immunosuppression is the most consistent risk factor for the development of BK viral infection and related BKVAN [189]. Population cohort studies have identified the use of T-cell depleting antibody, and tacrolimus and mycophenolate-based immunosuppressive regimen associated with a greater risk of BK viral infection, but other donor (e.g. BK-seropositivity of donor), recipient (age, male gender, presence of diabetes), and transplant-related risk factors (e.g. HLA-matching, acute rejection, DGF) have also been shown to be associated with BKVAN [190, 191]. In a prospective multicenter RCT of 682 kidney transplant recipients, cyclosporine--mycophenolic acid (MPA) regimen was associated with almost a 70% reduction in the risk of BK viremia at 12 months post-transplant compared to tacrolimus-MPA regimen, showing for the first time the differential relationship between CNI type and risk of BK viral infection [192].

Primary infection of BK virus is often subclinical, with the virus remaining latent in renal tubular epithelial cells and uro-epithelium. As a result of immunosuppression, BK viral replication may occur, resulting in BK viruria and viremia, and if untreated up to 10% of patients can pro-

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Table 58.3 Risk of disease recurrence after kidney transplantation.

	Risk of recurrence	Early recurrence ≤12 months	Late recurrence >12 months	Treatment options	Repeat transplantation[a]
Primary GN					
IgA nephropathy				IS	Yes
Primary FSGS				PP + IS	Cautious
Membranoproliferative GN				PP + IS	Cautious
Idiopathic membranous GN				IS	Yes
Presumed/advanced GN				Unknown	Yes
Secondary GN					
Atypical hemolytic uremic syndrome				Eculizumab	Yes, with eculizumab
Systemic lupus erythematosus				IS	Yes
Sjogren's syndrome				IS	Yes
Antiglomerular basement membrane disease				PP + IS	Yes
Vasculitis				IS	Yes
Infection (hepatitis)				Treat infection	Yes
Familial GN					
Alport syndrome[b]				PP + IS	Yes
FSGS				Unknown	Unknown
Polycystic kidney disease				Unknown	Unknown
Systemic/metabolic					
Oxalosis				None	Combined liver-kidney transplant
Diabetic nephropathy				Treat diabetes	Yes
Fabry's disease				Unknown	Unknown
Amyloidosis				IS	Cautious
Cystinosis				Unknown	Unknown

black, no risk; pink, low risk; orange, medium risk; red, high risk.
FSGS, focal segmental glomerulosclerosis; GN, glomerulonephritis; IS, immunosuppression; PP, plasmapheresis.
[a] Opinion-based recommendation.

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gress to BKVAN [193]. In the absence of effective treatment strategies for BKVAN, screening for BK viral replication (i.e. presence of decoy cells, BK viruria or viremia) is critical to facilitate early intervention prior to the development of overt BKVAN. The true incidence of BK viral infection remains unclear, but prospective screening studies have shown that the peak incidence of BK viremia occurred at 3 and 12 months post-transplant (up to 11–28%), with the majority of BKVAN occurring within the first 12 months post-transplant [193–195]. The optimal and most cost-effective screening method for BK viral replication remains unclear, although the test performances of urinary haufen and BK viremia screening methods appear to be superior to other screening methods [196–198]. As new onset BK viral infection tends to occur within the first 24 months post-transplant, the general recommendation is to consider regular screening for BK virus from 1 month up to 24 months post-transplant, with the frequency and duration of screening determined by the prevalence of the BK viral infection/BKVAN in each transplant center [199]. Renal allograft biopsy remains the gold standard for the diagnosis of BKVN and should be considered in the presence of sustained BK viremia (particularly if serum BK viral load >4 log copies/ml). There is currently no universal grading system for BKVAN and although each of these grading systems is slightly different, the presence of severe inflammation and fibrosis is consistently associated with poorer allograft prognosis. Nevertheless, the establishment and validation of a single standardized grading system for BKVAN will be important to guide treatment (and response to treatment in trial setting) and to assess prognosis [199–201].

The mainstay of treatment for BKVAN remains a reduction of the intensity of immunosuppression [202–204], but the optimal immunosuppressive regimen remains unknown. A dilemma facing clinicians is to decide the balance between reducing immunosuppression versus maintaining an adequate level of immunosuppression to prevent acute rejection (incidence of acute rejection post-immunosuppression reduction reported at 8–12%). As interstitial inflammation is a common histological finding in patients with BKVAN, clinicians are often reluctant to consider aggressive reduction of overall immunosuppression. If allograft failure attributed to BKVAN ensues, retransplantation is largely successful, but requires close monitoring for recurrent BK viremia [199]. Allograft nephrectomy is generally advocated prior to retransplantation in an attempt to reduce the latent BK virus load within the failed allografts urothelium. A management flow-chart of the diagnosis and treatment of BK viral infection and BKVAN is shown in Figure 58.2.

There is inconclusive evidence as to the efficacy of adjunctive treatment options for BKVAN, including the use of leflunomide and cidofovir. In a systematic review comprising 40 studies (RCT, case series, prospective, and retrospective cohort studies) examining the effect of immunosuppression reduction alone or in combination with other treatment strategies, the addition of the adjunctive therapies including intravenous immunoglobulin, leflunomide, cidofovir or ciprofloxacin did not alter the observed rate of allograft failure. However, the quality of the evidence was poor, with the estimates provided predominantly from uncontrolled case series [205]. A summary of the available treatment options for BKVAN is given in Table 58.4.

Severity of BK infection	Decoy cells/BK viruria	BK viraemia	Class A BKVAN	Class B BKVAN	Class C BKVAN
Likelihood of kidney kidney dysfunction	None	None/Mind	Mild/Moderate	Moderate	Moderate/Severe
Risk of allograft failure	0% →				70%
Treatment strategies:					
Observation	+	–	–	–	–
Reduction IS	–	+	+	+	+
Antibiotics	–	+/–	+	+	+
Leflunomide	–	+/–	+	+	+
Cidofovir	–	–	+/–	+	+/–
IVIg	–	–	–	+	+/–

Figure 58.2 Management algorithm for BK viral infection and BK viral allograft nephropathy. IS, immunosuppression; BKVAN, BK viral allograft nephropathy; IVIg, intravenous immunoglobulin.

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Table 58.4 Treatment options and level of evidence for BK viral allograft nephropathy.

Treatment options	Mechanism of action	Adverse events	Level of evidence
Essential treatment			
Reduction of immunosuppression	Improving cellular and humoral immune responses ± in vitro inhibition of BK viral replication	Increase risk of acute rejection	
Target lower CNI levels	Improving cellular and humoral immune responses	Increase risk of acute rejection	
Reduce MMF dose	Improving cellular and humoral immune responses	Increase risk of acute rejection	
Target lower CNI levels and reduce MMF dose	Improving cellular and humoral immune responses	Increase risk of acute rejection	
Change tacrolimus → cyclosporin	Improving cellular and humoral immune responses	Increase risk of acute rejection	
Change MMF → azathioprine	Improving cellular and humoral immune responses	Increase risk of acute rejection	
Change MMF → leflunomide	Improving cellular and humoral immune responses + in vitro inhibition of BK viral replication	Increase risk of acute rejection + adverse events of leflunomide (hemolysis, abnormal liver function, thrombocytopenia)	
Change to mTORi-based regimen	Improving cellular and humoral immune responses + in vitro inhibition of BK viral replication	Increase risk of acute rejection + adverse events of mTORi (mouth ulcers, oedema, proteinuria, pneumonitis)	
Combination of above	Improving cellular and humoral immune responses + in vitro inhibition of BK viral replication	Increase risk of acute rejection and other drug-specific adverse events	
Discretionary treatments			
Cidofovir (low dose)	in vitro inhibition of BK viral replication	Nephrotoxicity, peripheral oedema, proteinuria, uveitis, neutropenia, metabolic acidosis	
Brincidofovir	in vitro inhibition of BK viral replication	Gastrointestinal adverse events	
Fluroquinolone (ciprofloxacin and levofloxacin)	in vitro inhibition of BK viral replication	Possible emergence of bacterial resistance, headache, skin reactions, Achilles tendon rupture, gastrointestinal intolerance	
Intravenous immunoglobulin	Immuno-modulatory (neutralizing anti-BK virus antibodies and interaction of Fc fragment of pooled IgG antibodies with Fcγ receptors of target immune cells)	Possible paradoxical increase in viral load, thrombo-embolic complications, constitutional symptoms	
Adoptive T-cell therapy	BK-reactive cytotoxic T cells	None	

black, good level of evidence; orange, medium risk; gray, poor level of evidence.

Conclusion

Even though short-term allograft survival has substantially improved over the last few decades, early surgical and medical complications are not infrequent and can result in significant morbidity and adversely impact on longer-term allograft and patient outcomes if unrecognized or inadequately treated. This chapter has highlighted the potential complications that clinicians should be cognizant of within the first 12 months post-transplant, emphasizing the importance of undertaking vigilant surveillance and clinical monitoring to identify and treat these early transplant-related complications.

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Infections After Kidney Transplantation

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Introduction

Kidney transplantation requires significant immunosuppression to maximize graft outcomes and reduce the risk of rejection.

Infection post-transplantation can be either routine infections, as experienced by nonimmunosuppressed patients, or true opportunistic infections (OIs), mostly experienced by immunocompromised patients. Immunosuppression should be tailored according to immunological risk, as all patients who receive a transplant should weigh up the risk for rejection versus the risk for opportunistic infection.

Infection can be further classified as donor-derived or nondonor-derived. Detection of donor-derived infections may be well after the transplant has taken place or may be early after transplantation (within weeks to months). It is also possible for solid organ recipients to experience a reactivation of an infection that occurred prior to transplantation.

The physician identifying the donor and working up both donor and recipient should bear in mind the risk of these different infections based on timing in relation to transplantation and make informed choices about infection avoidance, prophylaxis, and early and late treatment options. In live donor transplantation, there is more capacity to consider and discuss these issues. All donors should be assessed for infectious risk.

In general, transplant patients should be treated aggressively and early to avoid poor clinical outcomes. Evidence for this is not always available in the form of randomized trials and is based on case studies and meta-analysis of previous reports in the literature. Immunosuppressed patients often lack the usual clinical responses such as fever or raised white cell count.

Definitions

Community-acquired Infection

The lack of a valid standard approach for defining sepsis makes it difficult to determine the true incidence of community-acquired infection and sepsis. Differences in case ascertainment contribute to the variation in reported incidence of community-acquired infection and sepsis. A working definition would be the presence of a positive blood culture and systemic inflammatory response syndrome (SIRS) before or within 48 hours of hospital admission [1].

Hospital-acquired Infection

Hospital-acquired infection is defined as an infection present at hospital admission or within 48 hours after admission in patients that fulfilled any of the following criteria:

- received intravenous therapy at home, wound care or specialized nursing care through a healthcare agency, family or friends, or had self-administered intravenous medical therapy in the 30 days before the infection (excluding patients whose only home therapy was oxygen use)
- attended a hospital or hemodialysis clinic or received intravenous chemotherapy in the previous 30 days
- were hospitalized in an acute care hospital for two or more days in the previous 90 days
- resided in a nursing home or long-term care facility [2].

Opportunistic Infection

Most studies reporting opportunistic infection (OI) lack a formal definition of this term and when present, heteroge-

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neity between studies was noted with regard to the types of infections considered or reported as opportunistic.

In a large systematic review, pathogens and/or specific presentations of certain pathogens were considered an OI, as they indicate an alteration in host immunity [3]. This list is included as.

Epidemiology

Previous exposure to pathogens is very important, both for the recipient but also for the organ donor. Transmitting a donor organism to a recipient might result in a donor-derived infection. The physician needs to have a clear understanding of this risk for the recipient and has to weigh up the potential benefit of the organ against this risk. In cases of deceased donation the risk for the donor does not need to be considered. In the case of a living donor the health of the person who donates the organ should be considered first.

Transplant patients are at normal to slightly higher risk of contracting community-acquired infections. These include viruses, bacterial, and fungal infections.

Respiratory Viruses

Influenza

Influenza is usually a community-acquired infection [4]. Vaccine immunogenicity for influenza in immunocompromised patients is low. Consideration should be given to vaccination in all transplanted patients.

Other Respiratory Viruses (Respiratory Syncytial Virus, Adenovirus, Parainfluenza)

Several clinical cases have been reported but no specific studies have been done [5]. Incidence is reported to be higher in immunocompromised patients.

Chikungunya, Dengue, and Zika

In endemic areas, the assessment of epidemiological risk is mandatory [6]. Donor deferral for 120 days in suspected or confirmed ZIKV+ has been recommended, while CHIKV+ donors should wait 30 days. No deferral is recommended for DENV+ donors. Evidence is based on individual case studies.

Bacterial Infections

Bacterial Pneumonia

Bacterial pathogens are the most frequent cause of pneumonia after transplantation [7]. Early after transplantation, recipients are at higher risk for nosocomial infections. The most commonly encountered pathogens during this period are gram-negative bacilli (*Klebsiella pneumoniae*, *Escherichia coli*, *Pseudomonas aeruginosa*), but gram-positive coccus such as *Staphylococcus aureus* or *Streptococcus pneumoniae* and anaerobic bacteria can also be found.

Six months after transplantation, pneumonias are mostly due to community-acquired bacteria (*S. pneumonia*, *Haemophilus influenza*, *Mycoplasma*, *Chlamydia*, and others).

Opportunistic pathogens take advantage of the state of immunosuppression, which is usually highest from 1 to 6 months after transplantation. During this period, but also occurring many years later in the setting of a chronically depressed immune system, bacterial pathogens with low intrinsic virulence can cause pneumonia.

Community-acquired Pneumonia Secondary to Intracellular Pathogens

Intracellular bacteria are common causes of community-acquired pneumonia (CAP) in immunocompromised patients [8]. There is considerable variation in the reported incidence between countries and change over time. The intracellular pathogens that are well established as causes of pneumonia are *Legionella pneumophila*, *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*, *Chlamydophila psittaci*, and *Coxiella burnetii*.

Gastrointestinal Infections

Common Organisms Affecting the Gastrointestinal Tract

Diarrhea is one of the most commonly occurring diseases in immunocompromised patients [9]. Patients suffering from diarrhea should be considered for salmonellosis, shigellosis, and *Campylobacter* infections, as well as infections with pathogenic *E. coli* strains, yersiniosis, and cholera. Diarrhea caused by toxigenic *Clostridium difficile* strains has a severe impact in immunocompromised patients.

Fungal Infections

Histoplasma capsulatum

Histoplasma capsulatum is a dimorphic fungus that most often causes asymptomatic infection in the immunocompetent population [10, 11]. In immunocompromised patients, it is likely to cause severe life-threatening infection. Incidence is rare (≤1%) and may result from endogenous reactivation of latent infection, de novo post-transplant acquisition, or donor-derived infection. Disseminated infection is common. Fever is the most common symptom and clinical features are often nonspecific, but patients with disseminated infection may present with a septic picture. Other features, including pancytopenia and hepatosplenomegaly, may not be prominent early in the course of

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illness. Routine screening of donors and recipients is not currently recommended.

Coccidioides

Donor-derived coccidioidomycosis causes unexpected morbidity and mortality in transplant recipients. Six reports of proven or probable coccidioidomycosis in immunocompromised patients were reviewed in a meta-analysis published in 2016 [12]. In four of the six studies, the infection was first detected at autopsy in the recipient. In two cases it was first identified in the donor. Twenty-one recipients received organs from these six donors. Transmission occurred in 43% at a median of 30 days post-transplant with a mortality rate of 28.5%.

Other Invasive Fungal Diseases

Opportunistic fungal pathogens such as *Aspergillus*, *Candida*, *Cryptococcus*, *Rhizopus*, and *Pneumocystis jiroveci* are distributed worldwide and constitute the majority of invasive fungal infections in immunocompromised patients [13]. Dimorphic fungi such as *Histoplasma capsulatum*, *Coccidioides* spp., *Paracoccidioides* spp., *Blastomyces dermatiditis*, *Sporothrix schenckii*, *Talaromyces (Penicillium) marneffei*, and *Emmonsia* spp. are geographically restricted to their respective habitats and cause endemic mycoses. Disseminated histoplasmosis and *T. marneffei* infection are recognized to cause a high rate of morbidities and mortalities in immunocompromised patients.

Mold Infections

Mold infections carry a substantial risk in solid organ transplant recipients, with a high overall mortality of near 30% [14]. The most important pathogens include *Aspergillus*, the Zygomycetes, *Fusarium*, *Scedosporium/Pseudallescheria*, and the dematiaceous (dark) molds. Risk factors for the infections vary by transplant type but include a degree of immune suppression and loss of skin or mucosal integrity. Correct diagnosis usually requires histopathology and/or culture. Management often requires a multidisciplinary team approach with combined antifungal and surgical therapies.

Other Pulmonary Opportunistic Infections

Tuberculosis

Solid organ transplant recipients are at an increased risk of tuberculosis [15]. Tuberculosis after solid organ transplantation generally occurs after months or years; early infections should raise the possibility of donor-derived infections. Tuberculosis is endemic in certain geographical areas and in these areas clinicians should have a low threshold to screen.

Cytomegalovirus

Human cytomegalovirus (CMV) represents the most common infection among recipients of solid organ transplants [16–19]. CMV disease ranges from asymptomatic viremia to CMV syndrome, to tissue-invasive disease. As CMV prophylaxis, treatment, diagnostics, and overall awareness have improved, the general trend has been toward earlier diagnosis of CMV disease and more mild clinical presentations in solid organ transplant recipients.

Previous meta-analysis showed 0.8% of solid organ transplant recipients developed CMV disease whilst receiving valganciclovir prophylaxis.

Donor-derived Infection

Donor-derived infections are important as they might give more severe and serious complications in recipients [20]. Screening potential donors for infection remains crucial to improving the safety of organ transplantation.

Donor-derived infection is usually suspected in the first 6 weeks after the transplant. As the immunocompromised recipient received an organ carrying an infection, there is an increased risk of developing systemic symptoms and diseases secondary to this event.

It is especially important to consider whether there is any multidrug-resistant organism that could potentially infect the recipient. Donors may also harbor latent infections (e.g. *Histoplasma*, *Coccidioides immitis*, *Mycobacterium tuberculosis*, and strongyloidiasis) based on their epidemiologic exposures.

Recommended Minimum Screening Policy for all Donors

- Serology for human immunodeficiency virus (HIV), hepatitis B, and hepatitis C (repeat within 28 days of donation in living donors)
- CMV IgG
- Epstein-Barr virus IgG
- HIV-1/2 antibody or HIV antigen/antibody assay
- Hepatitis B surface antigen and core antibody; consider nucleic acid testing (NAT)
- Hepatitis C NAT
- Syphilis screening
- Toxoplasma IgG
- Blood, urine, and sputum cultures

Recommended Additional Screening

- Tuberculosis screening (purified protein derivative or interferon-γ release assay)
- Testing based on prior history of living in an endemic area

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- *Strongyloides* antibody
- *Trypanosoma cruzi* antibody
- *Histoplasma* antibody
- *Blastomyces* antibody
- *Coccidioides immitis* antibody
- Hepatitis E antibody

- Testing based on epidemiologic exposures
  - *Brucella* antibody
  - *Cryptococcus* antigen
  - West Nile virus antibody

- Organ-specific testing: urine culture for kidney donors, bronchoalveolar lavage fluid/sputum culture for lung donors

Pathophysiology

Patients with bacterial infections have an increased risk of developing systemic symptoms, including sepsis and septic shock. Urinary tract and chest infections are common and prognosis in immunocompromised patients is similar to nonimmunosuppressed patients if treated early and correctly [21, 22].

An important risk factors for bacterial as well as fungal infections is neutropenia. Resistance rates against antibiotic vary between regions, especially for *E. coli*, *K. pneumonia*, and *P. aeruginosa*. Resistance rates should be carefully assessed in each region when antibiotic therapy is chosen.

Immunosuppressive therapy has dramatically reduced the incidence of acute rejection and improved graft survival in kidney transplant patients. However, viral infection as well as tuberculosis secondary to T-cell depleting therapy remains an important issue. T-cell depleting therapy may induce prolonged CD4 T-cell lymphopenia and trigger lymphocyte activation in some patients. Transplanted patients have an increased susceptibility to chronic viral challenges secondary to these immune alterations [23, 24].

In all immunocompromised patients the reactivation of latent infections remains an important consideration. This is especially important in the case of *M. tuberculosis*. The immune system seeks to control the infection by containing the bacteria in a granuloma, where it is exposed to stressful anaerobic and nutrient-deprived conditions. It is thought to be these environmental conditions that trigger the nonreplicating persistent state. A number of in vitro models have been developed that mimic conditions within the granuloma to a lesser or greater extent. These different models have all been utilized for the research of different characteristics of NRP *M. tuberculosis*, however their disparity in approach and physiological relevance often results in inconsistencies and a lack of consensus between studies [25].

Diagnosis

Clinical diagnosis can be more difficult in immunocompromised patients as they are usually slower to respond to pathogens with signs of inflammation and fever. Radiological investigations, nuclear medicine, and magnetic resonance imaging (MRI) might be useful to the clinical decision maker.

Blood tests involve:

- serological testing
- immuno assays
- antigen-based tests
- enzyme-linked immunosorbent assays
- nucleic-based acid-based test
- polymerase chain reaction.

Cultures remain the mainstay for diagnostic purposes, although patients often need treatment before culture results are available. Clinicians are advised to start broad-spectrum treatment while waiting for specific results and then narrow the treatment down to be as specific to the organism as possible. Routine tissue, blood, and urine culture can be extremely helpful.

Treatment

Transplant patients often have foreign material present in the form of dialysis liners, stents, and catheters. It is advisable to remove these as early as possible. Surgical management of collections, obstructions, or leaks is very important and should be done early, as patients deteriorate quickly because of their immunosuppressed status.

Reduction of Immunosuppression

To prevent infections flaring up or in the case of severe sepsis, patients might require a reduction in immunosuppression. This should be done with caution as it might result in a rejection episode.

Resistance Rates and Choice of Antibiotic if Resistance Is Suspected

Empirical antibiotic treatment is always needed in immunocompromised neutropenic patients. Consider treating with an antibiotic that will cover *P. aeruginosa*. Monotherapy regimens can be cefepime (ceftazidime), piperacillin/tazobactam or meropenem. Combination therapy could include a combination of aminoglycoaside (amikacin), glycopeptide (vancomycin), and a quinolone (ciprofloxacin) [26]. Although resistance rates vary across

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Table 59.1 Resistance rates reported in the literature for common gram negative bacteria [25–31].

Organism	ESBL (%)	Cefepime (Ceftazidime) (%)	Piperacillin/ Tazobactam (%)	Carbapenem (Meropenem)	Multiresistant (%)	Overall incidence of resistance
Escherichia coli	11–69	30–85	0–51	0–18%		21% (18–46%)
Klebsiella pneumoniae	23–69	50–71	25–63	0–31%		11% (4–20%)
Pseudomonas aeruginosa				44% (3–66%)	30–70	10% (3–30%)

different regions, a summary form the literature is given in Table 59.1 [27–33].

Influenza

There is low evidence that influenza vaccine has demonstrated effectiveness in reducing severe disease in immunosuppressed patients. Various strategies to improve influenza vaccine immunogenicity have been attempted, including two vaccine doses in the same influenza season and intradermal, adjuvanted, and high-dose vaccines. The timing of influenza vaccine is also important to achieve optimal immunogenicity. Given the suboptimal immunogenicity, family members and healthcare professionals involved in the care of these populations should be vaccinated. Healthcare professional recommendation for vaccination is an important factor in vaccine coverage.

Conclusions

It is difficult to make recommendations over a wide spectrum of infections as every infection could possibly warrant a meta-analysis on its own. However, certain key principles are important:

- Treatment should start early and be empirical.
- Remove all sources of infection, such as foreign material, stents, or collections, at an early stage.
- Immunosuppressed patients deteriorate rapidly and treatment should be aggressive.
- Assess the specific infection after cultures and sensitivity, and adjust antibiotic treatment accordingly as early as possible.
- Always consider donor-derived infection and if suspected all other recipients from the same donor should be considered for treatment.

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Part 10

Electrolytes and Acid-Base Disorders

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Electrolyte Disorders

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Introduction

- Electrolytes are involved in numerous intra- and extracellular biological and physiological functions, including maintenance of cell volume, cellular ionic strength, and enzymatic activities, critical for sustaining life. A narrow physiological range for each electrolyte is actively secured by multiple, often overlapping, regulatory and homeostatic systems, ensuring an optimal cellular and extracellular ionic environment for normal tissue and organ function. It is not surprising that most electrolyte alterations are associated with increased morbidity and mortality.
- Hyponatremia is by far the most common electrolyte disorder encountered in practice. Hyperkalemia is among the most common electrolyte disorders in patients with impaired kidney function. The prevalence of dysmagnesemia is unclear but is likely underdiagnosed as magnesium (Mg^{2+}) intake is insufficient in ~60% of the US adult population [1]. Advances have been made in understanding the underlying pathogenesis and in the management of these electrolyte alterations. This chapter will integrate existing and new advances in the area.

Dysnatremia

Definitions

Hyponatremia is defined as a serum $[Na^+] < 135$ mmol/l. Based on the measured blood osmolality, hyponatremia can be categorized as hypotonic, isotonic, or hypertonic hyponatremia. Hypotonic hyponatremia can be further divided into hypovolemic and euvolemic or hypervolemic hyponatremia. Serum $[Na^+]$ in the range 125–129 mEq/l is, in general, considered moderate and <125 mmol/l is considered severe hyponatremia.

Differentiating acute hyponatremia (developing within 48 hours) versus chronic hyponatremia (having hyponatremia for >48 hours) is critical. Rapidity in the development and severity of hyponatremia dictates the clinical manifestations. All of the above groupings are critical parts of diagnosis and directly impact the treatment strategy.

Hypernatremia is defined as a serum $[Na^+] > 145$ mmol/l. It occurs when total body water is disproportionately reduced in relation to extracellular fluid Na^+. Hypernatremia can result from pure water loss (e.g. diabetes insipidus [DI, central or nephrogenic], large insensible losses), hypotonic fluid loss (e.g. gastrointestinal losses [diarrhea] and renal osmotic diuresis), or hypertonic Na^+ gain (e.g. hypertonic NaCl or $NaHCO_3$ administration). Hypernatremia may be hypervolemic, euvolemic or hypovolemic. Unlike hyponatremia in which a hypertonic or hyperosmolar state can potentially be present, hypernatremia nearly always predicts a hyperosmolar state. Ideally, serum $[Na^+]$ should be kept in the range of 138–142 mmol/l, as this range is considered most physiological [17].

Epidemiology

Hyponatremia is the most common electrolyte disorder in both the community-dwelling population [18] and in hospitalized patients [19], with occurrence rates of 8–15% and 44%, respectively [20]. It is well-known to be associated with increased morbidity and mortality [21]. The

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older adult population and women are more susceptible to hyponatremia. Hyponatremia can also occur following strenuous exercise, known as exercise-associated hyponatremia (EAH).

Hypernatremia is less common than hyponatremia, with a reported incidence of 1–3% in hospitalized patients [18, 22]. At-risk populations include pediatric, older adult, and critically ill patients. One study showed that in the last two decades, the incidence of hypernatremia in critically ill patients has doubled [23], possibly related to more frequent use of loop diuretics and high concentration Na^+-containing fluids. Patients with chronic kidney failure (CKD) are, in general, considered to be at a higher risk of dysnatremia than the general population due to diminished glomerular filtration rate (GFR) and impaired tubular regulation [24]. With kidney disease progression from stage 1 to stage 5 (nondialysis), the incidence of hyponatremia declines slightly, while that of hypernatremia increases [24].

Clinical Manifestations

The clinical manifestations of hypo- and hypernatremia depend on the rapidity of the development and magnitude of $[Na^+]$ alterations [25, 26]. The brain is the dominant organ manifesting morbidity of hypo- and hypernatremia due primarily to the rigid confines of the brain and exquisite sensitivity of neurons to volume change (shrinkage or swell). When developing gradually (in days), the clinical manifestations of hyponatremia can be subtle, ranging from headache, lethargy, and restlessness to gait disturbance. When developed more rapidly or severe ($[Na^+] < 125$ mEq/l), confusion, respiratory distress, seizures, coma, and death can ensue [27]. Hypernatremia can manifest as excessive thirst, lethargy, and irritability, and, when severe, can progress to muscle spasms, vomiting, dyspnea, seizure, coma, and death. Delayed treatment of dysnatremia can cause irreversible neurological sequelae and increased mortality.

Pathophysiology

Sodium and Water Regulation

Serum Na^+ concentration represents water balance and is the primary determinant of serum osmolality. In the kidney, arginine vasopressin (AVP) and tonicity enhancer element binding protein (TonEBP, also known as transcription factor nuclear factor of activated T-cells 5, NFAT5) independently and synergistically regulate water absorption, maintaining serum $[Na^+]$ in the range 135–145 mEq/l. In addition to regulating water absorption, AVP also retains Na^+, thus influencing volume balance.

AVP binds to V2 receptors in the basolateral membrane of the collecting ducts and activates adenylyl cyclase-mediated cyclic AMP (cAMP) generation and protein kinase A-mediated signaling pathways, leading to phosphorylation and the apical membrane insertion of aquaporin 2 (AQP2) water channels. This, in turn, causes water absorption from tubular lumen to the circulation, driven by the tubulomedullary osmotic gradient. TonEBP, responding to increasing extracellular interstitial tonicity, forms homodimers. The latter preferentially binds TonE (tone consensus sequence) in its target gene promoters to increase the transcription of the target genes, including those involved in the synthesis and transport of organic osmolytes [28]. When activated, both AVP and TonEBP increase AQP2 gene expression and apical membrane AQP2 distribution. The stabilizing effect of organic osmolytes allows medullary tubular cells under osmostress to survive and perform vital functions. Excessive water absorption due to hyperactivation of the above water absorption system leads to the development of hyponatremia. On the contrary, mutations in the V2 receptor and AQP2 genes and acquired dysfunction of these proteins (e.g. chronic lithium exposure) can cause nephrogenic DI [3, 29].

On a high-salt diet (≥12 g/day), healthy adults are able to raise the amount of urine Na^+ excretion, typically without triggering extra water intake (lacking thirst stimulation) [30]. The kidneys are responsible for the excretion of concentrated Na^+ and simultaneously conserve water. This process requires the kidneys to absorb extra Na^+ and urea from tubular fluids to strengthen the intramedullary hypertonicity to facilitate water absorption/conservation. Indeed, recent studies show that a high-salt diet activates an array of metabolic processes, including enhanced hepatic urea genesis and muscle catabolism through at least in part activating glucocorticoid receptors [30, 31]. Also seen in association with a high-salt diet is elevation of circulating AVP. AVP is known to causes intraglomerular hypertension, mesangial contraction, and proliferation and stimulates intrarenal activation of the renin-angiotensin-aldosterone system (RAAS) [32]. When persistent and habitual, these homeostatic adaptive processes can become maladaptive [33]. Consistently, a recent population-based study showed that plasma copeptin (a surrogate marker of AVP) is a predictor for the occurrence of CKD [34], a chronic disease of ~13.4% population worldwide [35]. With the advent of Na^+ imaging nuclear magnetic resonance [36], a volume-independent pool of Na^+ in the skin and muscle has been revealed; heavy epidermal and dermal Na^+ signal is associated with refractory hypertension and risk for cardiac hypertrophy [37, 38].

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Special Considerations

Female Susceptibility to Hyponatremia

Most, but not all, studies show a female susceptibility to hyponatremia and hyponatremia-associated symptoms. For example, females are more susceptible to hyponatremia among marathon runners [39]. On the other hand, conflicting results were shown regarding a female predilection for postoperative hyponatremia [40, 41], possibly related to varying degrees of stress and care styles. The potential mechanisms of female susceptibility include (i) inhibitory effects of estrogen on Na^+,K^+-ATPase, which reduces the cells homeostatic regulation in the setting of hypo or hypernatremia, (ii) lower muscle mass, which can reduce the buffering capacity for the water shift, (iii) lower baseline serum [Na^+] than their male counterparts, which renders serum [Na^+] in female easier to fall into a hyponatremic range, and (iv) more pronounced AVP-induced cerebral vasoconstriction than that in males, rendering females at a greater risk for reduced central nervous system oxygen delivery [42].

Exercise-associated Hyponatremia

Exercise-associated hyponatremia (EAH) in recent decades has become increasingly recognized [43, 44] following a number of death cases in athletes after strenuous exercise. It has become clear, however, that EAH can also occur in nonprofessional athletes and in association with a variety of physical exertions, including running, hiking, long-distance swimming, mountain cycling, weightlifting, and even tennis and yoga. Patients with cystic fibrosis are at increased risk and can develop EAH with low-intensity exertion [44]. Mechanisms of EAH are complex. Overconsumption of water plus nonosmotic (stress-related) AVP secretion are important contributors in the genesis of hyponatremia.

Symptoms of EAH include bloating, dizziness, mild nausea, headache, vomiting, progressing to confusion, dyspnea, altered mental status, obtundation, further progressing to seizure, coma, decorticating posturing, mydriasis, and death. These symptoms could occur shortly after exercise and, as detailed above, women tend to be more susceptible.

For symptomatic patients, intravenous administration of 3% NaCl (typically 100 ml every 10 minutes, several times) can effectively correct hyponatremia and eliminate the symptoms. Recent studies show that similar efficacy can be achieved through an equivalent amount of hypertonic saline given orally [2]. The oral sodium treatment resulted in a comparable blood [Na^+] increase but a higher degree of urine Na^+ excretion. There was no difference in plasma AVP in both groups pre- and postintervention, consistent with the known phenomenon of the nonsuppressible nature of stress-related AVP. Of importance, calculated plasma [Na^+] increase based on the best-known formula was 1.3 mEq/l with the amount of NaCl administration, markedly differing from the actual plasma [Na^+] changes, 2.0 ± 0.9 mEq/l in the intravenous group, and 1.9 ± 1.6 mEq/l in the oral group. These observations underscore the importance of avoiding the reliance on calculations but rather measuring [Na^+] to monitor the degree of [Na^+] correction. It also suggests the possibility of tissue Na^+ mobilization. Consistent data were reported recently [45] showing formulae cannot correctly predict [Na^+] change following a known quantity of high percentage saline loading in healthy adults.

The nonsuppression of AVP has been shown in hypo, euvolemic, and hypervolemic EAH. Among factors that cause nonsuppressible AVP could be interleukin-6 release, nausea, vomiting, and acute stress. There have been studies showing that patients on a baseline low-salt diet seem to be more susceptible to this condition, suggesting a role of tissue Na^+ load in the genesis of EAH. Consistently, overhydration contributes only in part to the EAH; hyponatremia can occur in euhydration even hypohydration states. Conversely, hypernatremia can develop in overhydration or the euhydration state. These observations again suggest a role of tissue Na^+ sequestration or release into the body fluids in the genesis of dysnatremia.

Hypernatremia indicates the presence of total body water deficiency in relation to body fluid Na^+. It can result from (i) loss of water or hypotonic fluid (loss of water > loss of Na^+) or (ii) gain of Na^+, such as receiving hypertonic saline or salt tablets without taking in water. Renal loss of water can be caused by diabetes insipidus, hypercalcemia, hyperglycemia, chronic hypokalemia, and medications such as loop and osmotic diuretics, lithium, and vasopressin V2 receptor blockers. Hypernatremia can also be caused by water loss from the gastrointestinal tract due to osmotic diarrhea and vomiting. In the setting of excessive sweating or burns, skin loss of hypotonic fluids can be responsible for hypernatremia. Sustained hypernatremia is typically associated with lacking access to water or the presence of impaired thirst mechanism. The elderly, children, and critically ill patients are especially vulnerable to hypernatremia.

Special Consideration

Lithium-associated Kidney Effects

Lithium gains entry to renal epithelial cells through competing with Na^+. In the distal nephron, lithium enters renal tubular cells through the apical membrane epithelial sodium channels (ENaCs). Lithium has a 1.5–2-fold stronger affinity to ENaC, making it preferentially absorbed over Na^+ via the ENaC. Its exit from the cells is, however,

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not readily supported by Na^+,K^+-ATPase as lithium is a poor substrate for this ATPase. Lithium, therefore, accumulates in the renal epithelial cells, competing with Na^+ and Mg^{2+} for their protein binding and causing a variety of adverse cytotoxic effects through interfering with multiple cellular signaling pathways. One of the major effects of lithium is the inhibition of glycogen synthase kinase-3β (GSK3β), which relays the actions of aldosterone and AVP. The inhibition of GSK3β causes impairment of adenylyl cyclase activity, leading to reduced cAMP generation. GSK3β inhibition also releases the normally inhibitory effect of GSK3β on Cox-2, which causes hyperactivation of Cox-2 and a robust generation of prostaglandins. Both the reduction of cAMP and increased generation of prostaglandins impair renal water absorption, causing a nephrogenic type of DI.

Because lithium interferes with Na^+ reabsorption from tubular fluids, it compromises the maintenance of medullary concurrent mechanism and the steep osmotic gradient for renal water absorption. Increased solute content in the tubular fluids also enhances tubuloglomerular feedback (TGF), inducing constriction of afferent renal arterioles, and thus risking renal underperfusion and ischemia.

Patients on chronic lithium treatment have an increased risk for developing CKD. This phenomenon has been confirmed by epidemiological, clinical, and histopathological studies. Longer lithium use (>20 years), older age, and episodes of lithium intoxication are some of the risk factors for the development of lithium-induced nephropathy and CKD [46, 47]. CKD in patients on lithium is typically asymptomatic. Their blood pressure tends to be low normal or normal. Urine sedimentation is generally normal with and without proteinuria. Renal biopsy is typically characterized by evidence of tubulointerstitial fibrosis and multiple renal microcysts, and is often associated with focal segmental glomerulosclerosis. Interestingly, GSK3β is involved in the maintenance of primary cilia which, in its malfunction, contributes to kidney cyst formation, revealed in the investigation of polycystic kidney disease [48].

Renal monitoring for patients with chronic lithium exposure is important to assess the degree of polyuria, electrolyte and acid-base alterations, and kidney dysfunction. Preventive therapy (i.e. amiloride addition) to deter lithium entry to the renal epithelial cells has shown some encouraging results in terms of reducing the degree of polyuria [49, 50]. However, long-term effects of lithium exposure, especially with regard to lithium-associated CKD, have yet to be studied in detail. General guidelines for minimizing the risk of renal damage in lithium-treated patients include (i) monitor serum creatinine and estimated glomerular filtration rate (eGFR) regularly every 6 months to 1 year, and (ii) avoid lithium toxicity and maintain lithium levels at the lowest effective level and consider once-daily dosing. Lithium discontinuation and nephrology consultation should be considered when the serum creatinine reaches ~1.6 mg/dl (140 mmol/l).

Up to 30% of lithium-treated patients develop a mild degree of hypercalcemia. This tends to become problematic in patients with CKD and reduced capacity of urine calcium excretion. The underlying mechanisms for hypercalcemia are multiple, often associated with hyperparathyroidism related to either parathyroid adenoma or multinodular hyperplasia. Surgery for adenoma can be effective and cinacalcet treatment can be tried for patients with multinodular lesions. Hypothyroidism is another common adverse effect of chronic lithium exposure. Maintenance hormone replacement is the treatment of choice.

Significant Tests

For hyponatremia

Measurement of serum osmolality (normal serum osmolality: 275–295 mOsm/kg water) is required to determine the body-fluid tonicity and to rule out (i) pseudohyponatremia (isotonic hyponatremia) in the setting of hyperlipidemia and paraproteinemias, and (ii) hyperosmolar (>295 mOsm/kg) hyponatremia mostly in the setting of hyperglycemia or after mannitol or other solute administration. True hypotonic hyponatremia typically shows a reduced serum osmolality (<280 mOsm/kg).

For hypernatremia

As hypernatremia represents a hyperosmolar state, measurement of serum osmolality is generally not required. Urine osmolality is a useful test to differentiate renal water loss (e.g. diabetes insipidus, which is a state of inappropriately dilute urine) from extrarenal water loss (concentrated urine representing appropriate renal water conservation). Urine osmolality may not be informative in patients taking diuretics and with CKD.

For polyuria

Central DI, nephrogenic DI, and primary polydipsia can all present with polyuria and polydipsia. Central and nephrogenic DI, however, even at a compensated state, typically present with high normal levels of serum [Na^+] (>140 mEq/l) while primary polydipsia including beer potomania and psychogenic polydipsia typically present with low normal serum [Na^+] (<140 mEq/l).

DI tends to have more frequent nocturia compared to those with primary polydipsia. DI could be idiopathic, especially central DI (~50% of central DI cases are idiopathic). Nephrogenic DI could be due to medications

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(lithium being the most common cause) or genetic defects related to mutations in the genes encoding vasopressin V2 receptor or AQP2 channel [51].

To differentiate central vs. nephrogenic DI, a water deprivation study has classically been the test of choice. With water deprivation, if urine can concentrate to 800 mOsm/kg or greater in patients with conserved kidney function, DI is excluded. Polyuria in such patients is likely due to primary polydipsia. Patients tend to have a low normal serum [Na^+] as water-drinking drives the symptom. In patients who fail to concentrate urine despite serum [Na^+] elevation to ~150 mEq/l, a dose of desmopressin (typically 2 μg intravenously) is given to differentiate central vs. nephrogenic DI. If the patient's urine remains diluted (<300 mOsm/l) a diagnosis of nephrogenic DI could be made. However, if the patient is able to respond to a degree and urine concentrates ~300–500 mOsm/l, a partial central DI is present. For patients who are able to concentrate urine to >600 mOsm/kg in response to desmopressin, a diagnosis of central DI can be made. During the study, patients should be carefully monitored, and blood and urine should be sampled as often as every 30 minutes to 2 hours. Approximately 2–3% of weight loss is often present during the water deprivation.

In recent years, serum copeptin determination has emerged as a greatly simplified diagnostic test for DI. A baseline unstimulated (nonwater-deprived) serum copeptin level of >21.4 pmol/l in a polyuric patient is diagnostic for nephrogenic DI, with sensitivity and specificity of 100% [29], more accurate than the water deprivation study [52]. Copeptin response to hypertonic Na^+ administration demonstrates a superior diagnostic sensitivity and specificity in diagnosing central DI and in the differentiation of central DI from primary polydipsia [53].

Prognosis: Complications

Both hypo- and hypernatremia increase mortality [54–57]. In the community patient population, hyponatremia can be minimally symptomatic. Nonetheless, these patients, compared to eunatremic populations, tend to have a higher rate of all-cause mortality and a higher rate of fracture and its related morbidity [54, 55]. In hospitalized patients with mild hyponatremia, clinical settings seem to determine the patient outcomes [58]. In almost all comorbid settings (end-stage liver and with end-stage heart failure), occurrence of hyponatremia elevates mortality [56, 59]. Pulmonary edema in the setting of hyponatremia can be neurogenic. It may reflect central nervous system hypoxia and should be treated urgently, as combined hypoxia and hyponatremia impair brain adaptation, leading to worsening brain edema and can markedly increase mortality [60].

Hypernatremia carries a high rate of morbidity and mortality. In a large multicenter study of critically ill patients, Darmon et al. showed that fully adjusted 30-day mortality increases from 22.5% up to 54.5% from mild (145–150 mEq/l) to more severe hypernatremia [61]. In patients with acute cardiovascular disease, especially those with cerebrovascular accident, serum [Na^+] outside the range of 141–146 mEq/l has been shown to increase hospital and 28-day mortality [62, 63].

Treatment

Hyponatremia

For patients with volume depletion, restoration of volume with isotonic fluids should turn off AVP release, leading to renal water excretion and correction of hyponatremia. For patients with euvolemic hyponatremia, select appropriate treatment options (outlined in Table 60.1) based on clinical scenarios and identify the underlying causes (Table 60.2). Eliminating the causes will in general lead to the resolution of hyponatremia. A registry study involving 225 sites in the United States and European Union showed that initial treatment for hyponatremia often employs modalities of limited efficacy. A significant portion of hyponatremic patients discharged from hospital remained hyponatremic [64]. Hypervolemic hyponatremia typically occurs in patients with hepatic cirrhosis or congestive heart failure. Liver or heart transplant will eliminate the Na^+ abnormality. For exercise-induced hyponatremia, there has been no standard prophylactic measure to date. Forcing fluids is likely harmful and is not advised. In general, athletes are advised to drink to their thirst. Close monitoring and treating those with even mild symptoms and with biochemical hyponatremia are essential. Oral administration of hypertonic saline has recently been shown to be effective, convenient, and noninferior to intravenous administration of an equivalent amount of hypertonic saline [2]. Given the consequences of untreated hyponatremia in endurance runners and potential for progression (to obtundation, coma, and death), oral hypertonic saline seems advisable, especially in those with mild symptoms.

Regardless of the etiology, the rate of serum Na^+ correction depends on (i) whether the patient is symptomatic and (ii) onset rapidity (<48 hours or >48 hours). For symptomatic hyponatremia, the predominant current practice is 3% saline in 100–300 ml bolus administered intravenously over 10–45 minutes with the goal of raising serum [Na^+] by 4–5 mmol/l initially. Repeated bolus may be used when appropriate to achieve this goal [65, 66].

For patients with chronic hyponatremia (onset >48 hours) who are relatively asymptomatic, serum [Na^+] should be corrected slowly to prevent neurological damage such as

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Table 60.1 Evidence table: sodium disorders.

Treatment	Recommendation	Certainty of evidence	Strength of recommendation
Hyponatremia			
Hypertonic saline (3% NaCl)	For symptomatic hyponatremia, we recommend 100–300 ml 3% saline be given parenterally over 10–30 min with the goal to raise serum [Na+] by ~5–6 mEq/l Oral administration may have similar efficacy based on lower certainty evidence [2]	High	Strong
Isotonic fluids (0.9% saline or balanced fluids)	For patients with hypovolemia, we recommend that volume restoration with isotonic fluids diminishes AVP stimulatory force, and clinicians should avoid overcorrection of volume depletion	High	Strong
Oral water restriction (800 ml/day)	We recommend oral water restriction be used for patients with syndrome of inappropriate antidiuretic hormone (SIADH) or other euvolemic and high volume hyponatremia Clinicians should be aware of low patient adherence and that restriction will not be sufficient when urine osmolality is >500 mOsm/kg, or the sum of urine Na^+ and K^+ is >serum [Na^+], water restriction alone will not be sufficient Additional measures will be required	Moderate	Strong [3]
Eliminate causes	We recommend that agents with hyponatremic potential should be replaced or discontinued if possible (e.g. hydrochlorothiazide, antidepressants [mainly selective serotonin reuptake inhibitors], anticonvulsants, antipsychotics, cytotoxic agents, pain medications [4], ecstasy) For patients with cancer as the cause of hyponatremia (e.g. small cell lung cancer), treatment should be focused on cancer eradication in addition to the other corrective strategies outlined in this table (treatment plan should be individualized)	High	Strong
Salt tablets + oral furosemide	We recommend that salt tablets combined with oral furosemide be used for euvolemia patients refractory to the above measures	Moderate	High
Vaptans (V1A/V2R antagonist Conivaptan; V2R antagonists Lixivaptan, Mozavaptan, Satavaptan, Tolvaptan)	We suggest avoiding use of vaptans for symptomatic hyponatremia due to the risk of overcorrection, even at lower than 15 mg/day dosage [5] We suggest avoiding use of vaptans for hypovolemic hyponatremia We suggest vaptans may be tried for SIADH and other euvolemic and hypervolemic hyponatremia refractory to other measures and should not be expected to be used long term (>1 month) We suggest watching for overcorrection and other adverse effects with vaptan therapy, including liver dysfunction [6, 7]	High	Low to moderate [8]
Urea, oral administration	We suggest urea (oral administration) is useful for critically ill [9] and subarachnoid hemorrhage [10, 127] patients We suggest oral urea administration may be effective for chronic milder and relatively asymptomatic hyponatremia We suggest oral urea may have similar efficacy and tolerability to vaptans [11]	Moderate	Moderate
Intravenous DDAVP + dextrose if serum [Na^+] is overcorrected (typically >8 mEq/day)	We recommend intravenous DDAVP + dextrose be used if serum sodium is overcorrected (typically >8 mEq/day) if water alone is insufficient to slowing the rate of correction We recommend that the 24-h serum [Na^+] increment (not hourly increment) is critical and should be ~6 mEq/l within the first day for chronic hyponatremia	Moderate	Strong [12]
DDAVP IV + 3% saline	We suggest DDAVP + 3% saline be used when controlling the rate of [Na^+] correction	Moderate	Moderate [13, 14]

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Table 60.1 (Continued)

Treatment	Recommendation	Certainty of evidence	Strength of recommendation
Hyponatremia			
Lithium	We suggest lithium be considered in eu- and hypervolumic patients, although many patients may reasonably choose to refuse due to low certainty evidence and risk of multiple adverse events	Moderate	Weak [15]
Demeclocycline	We suggest demeocycline may be used in eu- and hypervolumic patients, although many patients may reasonably choose to refuse due to low certainty evidence, low onset of action, nephrotoxicity, unpredictable increases in sodium, gastric intolerance, and skin photosensitivity	Low	Weak [16]
Hypernatremia			
Isotonic fluids	We recommend isotonic fluids for patients with hypovolemia, as restoration of volume should take clinical precedence We recommend that once the volume is restored, hypotonic fluids should be initiated to correct hypernatremia	High	Strong
Hypotonic fluids	We recommend for patients with adequate volume, dextrose water or hypotonic Na^+-containing fluids be used (to account for ongoing Na^+ losses)	High	Strong
Diuretics + dextrose water or water	We recommend for patients with expanded volume a combination of diuretics (volume reduction) and dextrose water (or water) be used	Moderate	Strong

V1A/V2R; Vasopressin receptor subtypes V1a /V2; V2R Vasopressin receptor subtype V2; DDAVP diamino D-arginine vasopressin; SIADH syndrome of inappropriate antidiuretic hormone.

Table 60.2 Causes of euvolemic hyponatremia.

Severe hypothyroidism
Adrenal insufficiency
Low solute intake: beer potomania, tea and toast diet
Psychogenic polydipsia
SIADH

- Idiopathic/aging related
- Nausea/vomiting
- Pain
- Cancer (small cell lung cancer)
- Lung: abscess/empyema/chronic obstructive pulmonary disease
- Central nervous system: meningitis/encephalitis/ stroke
- Medications: antidepressents (mainly SSRIs), anticonvulsants, antipsychotics, cytotoxic agents, some pain medications [4], and rarely amiodarone
- Ecstasy (3,4-methylenedioxy-methamphetamine, MDMA)

osmotic demyelination syndrome (ODS) [129]. For patients with ODS risk factors, i.e. malnutrition, alcohol addiction, and hepatic cirrhosis, target serum [Na^+] increase should be in the range of 4–6 mEq/l in the first 24 hours. For those without the risk factors, target serum [Na^+] increase should be in the range of 6–8 mEq/l in the first 24 hours and should not exceed 18 mEq/l in 48 hours. In general, the magnitude of [Na^+] correction in 24 hours is more important than an hourly correction rate [67].

Inadvertent overcorrection is not rare. A recent study shows that the overcorrection rate in the first 24 hours is over 40% [68]. Younger age, being a woman, schizophrenia, lower Charlson comorbidity index, lower presentation serum sodium, and urine sodium <30 mEq/l are risk factors for rapid overcorrection [68]. Overcorrection should be reversed with either hypotonic fluids or deamino D-arginine vasopressin (DDAVP) combined with hypotonic fluids, preferably within 12 hours. DDAVP use was associated with effective slowing in the rate of [Na^+] correction in a retrospective study of 1450 patients admitted for severe hyponatremia (serum [Na^+] <123 mEq/l). Longer durations of hyponatremia and length of hospital stay, however, were noted [69]. For patients with a high risk for ODS, DDAVP could potentially be used to slow the rate of correction [68, 69]. Serial serum [Na^+] measurements (every 2–6 hours) are required to evaluate treatment adequacy, especially during the initial 24 hours. A role for urea in the management of overcorrection is under investigation [128].

Hypernatremia

Management of hypernatremia should start with assessing the patient volume status and eliminating or treating potential causes/contributors of hypernatremia. For patients with hypovolemia, isotonic fluids should be used to restore

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volume status. After euvolemic status is achieved, hypotonic fluids should be initiated to correct hypernatremia. The rate of correction depends on the rapidity of hypernatremia development. If hypernatremia is developed over 48 hours or of unknown duration, serum [Na^+] correction should not exceed 10–12 mEq/l in the first 24 hours. Overly rapid correction can cause cerebral edema [34]. On the other hand, acute (onset <48 hours) hypernatremia can be corrected more rapidly (up to 0.5–1.0 mEq/l per hour) when appropriate.

Correction of hypernatremia should be timely. Studies have shown that if hypernatremia fails to be corrected fully within 4 days, the rate of irreversible brain damage and mortality can increase considerably [70]. It is therefore advisable to complete the correction within 3–4 days.

Risk factors for demyelination include malnutrition, alcoholism, and liver failure. Brain compression due to parenchymal edema can cause neurogenic pulmonary edema and hypoxia [60]. Pulmonary edema in patients with symptomatic hyponatremia may thus signify pending herniation. The outcome could change with prompt treatment of hyponatremia [71].

Total body free water deficit in hypernatremia can be estimated by calculating estimated total body water (total body water = body weight × [0.6 for men, 0.5 for women]). It is important to recognize, however, that the osmo-active pool of body fluid Na^+ may not be static. Studies have revealed tissue (skin and muscle) storage pools of osm-independent Na^+ that can exert a role in the Na^+ homeostasis [37, 45, 72]. The rate and amount of water replacement in correcting dysnatremia should thus be based on repeated serum [Na^+] measurements. In one study, observed increase in [Na^+] exceeded the increase predicted by the calculation by 74.2% of the cases studied [73]. Reliance on existing formulae to predict [Na^+] correction should therefore be avoided. Frequent serum [Na^+] measurement is imperative.

Dyskalemia

Table 60.3 summarizes the quality of evidence and strength of recommendations for the various components of the management of potassium disorders.

Definitions

Hypokalemia is defined as a serum K^+ concentration [K^+] < 3.5 mEq/l, and hyperkalemia as serum [K^+] > 5.3 mEq/l. It is often further arbitrarily classified as mild (5.4 to <6 mEq/l), moderate (6 to <7 mEq/l), and severe (≥7 mEq/l) [86].

Epidemiology

While dyskalemia, hypokalemia, and hyperkalemia can develop in both normal and CKD populations, hyperkalemia occurs predominantly in patients with CKD. In a 2018 international meta-analysis of 1,217,986 (mean age 55 ± 16 years) subjects, followed up for an average of 6.9 years [87], the prevalence of reduced serum [K^+] was 23.6% (<4.0 mmol/l) and 1.91% (<3.5 mmol/l). The prevalence of [K^+] elevation in non-CKD individuals was 3.31% (>5.0 mmol/l) and 0.49% (>5.5 mmol/l). In patients with CKD, the prevalence of low [K^+] was 12.6% (<4.0 mmol/l) and 2.03% (<3.5 mmol/l), and prevalence of high [K^+] was 17.9% (>5.0 mmol/l) and 4.23% (>5.5 mmol/l).

Hyperkalemia develops most often in the settings of (i) reduced GFR, which is the most powerful determinant of hyperkalemia generation, (ii) increased K^+ intake (often in combination with GFR reduction), (iii) on medications that reduce kidney K^+ excretion (Table 60.4), (iv) hyperkalemic (type IV) renal tubular acidosis and voltage-dependent renal tubular acidosis, and (v) transcellular potassium shift, i.e. cellular/tissue breakdown in rhabdomyolysis and hemolysis, insulin deficiency, and hyperosmolar state.

Hyperkalemia is the most common electrolyte disorder in patients with CKD [86]. Its prevalence increases as CKD progresses [88]. In a nested case-control study of 180 diabetic and 180 nondiabetic CKD patients followed in a nephrology outpatient clinic [89], matched for gender, age, and eGFR, the prevalence of hyperkalemia was higher in diabetics CKD3 (28.6% vs. 17.5%, $P = 0.036$). In CKD4, it was equally high in both groups (35.5% vs. 32.3%, $P = 0.788$). In CKD4, the use of angiotensin-converting enzyme inhibitors (ACEIs; odds ratio [OR] 2.228, 95% confidence interval [CI] 1.254–3.958) and smoking (OR 2.254, 95% CI 1.218–4.171) were independently associated with hyperkalemia in fully adjusted models.

Diabetic patients are at high risk for hyperkalemia [88] due to a combination of (i) insulin deficiency, (ii) episodes of hyperosmolality related to hyperglycemia, and (iii) frequent occurrence of hyporeninemic hypoaldosteronism (type IV renal tubular acidosis). Patients with chronic urinary tract obstruction can develop defects in Na^+ absorption via ENaC in the collecting duct, leading to failure in the generation of the luminal negative voltage. The voltage defect impairs tubular K^+ and H^+ secretion, leading to hyperkalemic normal anion gap acidosis [90], known as voltage-dependent renal tubular acidosis. Such tubular defects can resolve with timely reversal of obstruction. Patients with a family history of hyperkalemia and salt-sensitive hypertension should be investigated for familial hyperkalemia and hypertension (FHHt) (also known as pseudohypoaldosteronism type II [PHA II] or Gordon syndrome) [91–93].

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Table 60.3 Evidence table: potassium disorders.

Treatment	Recommendation	Certainty of evidence	Strength of recommendation
Hypokalemia			
Increasing dietary K^+	We recommend increasing dietary potassium intake	High	Strong
Oral K^+ supplementation	We recommend oral potassium supplementation be used	High	Strong
IV K^+ supplementation	We recommend avoiding use of dextrose-containing solution for K^+ infusion We recommend a central line be used to infuse K^+ We recommend K^+ infusion should not exceed 10 mEq/h (if 10–20 mEq/h is deemed necessary, cardiac monitoring is required; >20 mEq/h is not recommended)	High	Strong
Hyperkalemia			
Multipronged: adjust dietary K^+	We suggest a low K^+ diet (<40 mEq/day) be used in combination with other strategies	Weak (no data on the efficacy of dietary counseling [74])	Strong
Medications For CKD: kidney and GI effects of RAAS inhibitors For dialysis patients: GI effects	We recommend that medication regimens be reviewed to minimize the exposure of drugs that may induce hyperkalemia We recommend avoiding hyperkalemic medications, but balance the relative pros and cons (e.g. RAAS inhibitors [75])	Strong	Strong
Intravenous Ca infusion	We recommend intravenous calcium be used to stabilize myocardium and prevent malignant cardiac excitability We recommend that other strategies are considered for longer-term effects on hyperkalemia be used in conjunction with intravenous calcium We recommend for digoxin-associated hyperkalemia that Ca^{2+} infusion not be used due to risk of cardiotoxicity and dysrhythmias [76]	Moderate	Strong
Insulin (intravenous route with glucose)	We recommend that insulin administered intravenously in combination with glucose be used for severe and symptomatic hyperkalemia We recommend low-dose intravenous insulin be used to reduce the occurrence of hypoglycemia in CKD and end-stage renal disease [77]	High	Strong
β2 receptor agonist (albuterol inhaler)	We suggest inhaled β2 receptor agonist be used for severe and symptomatic hyperkalemia	Moderate	Medium
$NaHCO_3$ infusion	We recommend sodium bicarbonate infusion be used when metabolic acidosis is present The clinician should be aware of the risk of volume overload, hypocalcemia (ionized form), and, when using undiluted, hypernatremia	Moderate	Strong
Loop and thiazide diuretics	We recommend that loop and thiazide diuretics be used to promote kaliuresis This evidence may be more applicable for patients with CKD [78] Clinicians should monitor for individual diuretic-associated adverse events	High	Strong

(*Continued*)

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Table 60.3 (Continued)

Treatment	Recommendation	Certainty of evidence	Strength of recommendation
Patiromer: oral agent, onset of action within ~7 h [79]	We recommend that patiromer (a nonabsorbable, Ca^{2+}-K^+ exchange polymer that selectively binds K^+ mainly in the colon) be used to treat chronic hyperkalemia in patients with nondialysis CKD Patients need to be aware of potential side effects, including constipation and mild hypomagnesemia and take the medication spaced at least 1 h apart from other medications due to a potential risk of drug–drug interaction	High	Strong [80, 81]
Sodium zirconium cyclosilicate: oral agent, onset of action within 2 h	We recommend that sodium zirconium cyclosilicate (a nonabsorbable, insoluble crystal that traps gut K^+ in exchange for Na^+ and H^+) be used to treat acute or chronic hyperkalemia in patients with nondialysis CKD Patients should be aware that edema is a potential side effect	High	Strong [82]
Kayexalate (sodium polystyrene sulfonate)	We suggest sodium polystyrene sulfonate be used to treat acute hyperkalemia as a temporizing measure Patients may reasonably choose not to take this medication due to low certainty evidence and multiple case reports of causing gut ischemia and necrosis	Low	Weak [83]
Fludrocortisone	We recommend fludrocortisone be used in selected patients with mineral corticoid deficiency and without a high risk of volume retention	Moderate [84]	Strong
Hemodialysis	We recommend hemodialysis be used for life-threatening, intractable, and refractory hyperkalemia	Strong	Strong
Oral glucose	We recommend oral glucose be used for nondiabetic hemodialysis patients [85]	Moderate	Strong

RAAS; renin-angiotensin-aldosterone system

Table 60.4 Commonly used medication known to induce hyperkalemia.

- RAAS inhibitors (angiotensin converting enzyme inhibitors, angiotensin receptor blockers, renin inhibitors)
- Mineralocorticoid receptor inhibitors (spironolactone and eplerenone)
- β2 receptor blockers
- K^+ sparing diuretics (triamterene, amiloride)
- Heparin (inhibiting aldosterone production)
- Digitalis glycosides (blocking Na^+-K^+-ATPase, impairing intracellular K^+ distribution)
- Calcineurin inhibitors (cyclosporine, tacrolimus)

The modern diet lacks sufficient K^+ [94]. Intake of less than the recommended 4.7 g (120 mmol/day) or a minimum of 3.5 g (~90 mmol/day) [95] is common due to a reduced consumption of plant foods (fruits and vegetables) [94]. The modern diet has a K^+/Na^+ ratio of ~0.4 whereas in the premodern era the ratio was >3 and often near 10. As plant foods are also a rich source of base or base-equivalents and fiber, a low K^+ diet is coupled with a net acid accumulation (positive net endogenous acid production) and sluggish bowel transit from lacking fiber, which can alter gut microbiota [96]. In healthy adults, mild or low-normal serum [K^+] is common and could be linked to risks of many common and noncommunicable chronic diseases [33]. In addition to diet, kaluretic diuretic use (furosemide, hydrochlorothiazide, and osmotic diuresis), alkalosis, and hypomagnesemia can exacerbate K^+ depletion. Vomiting and diarrhea associated with acute illness can superimpose on the baseline deficiency and cause clinically significant hypokalemia. Patients with hypertension and hypokalemia should be investigated for primary hyperaldosteronism (Conn's syndrome). Persistent or recurrent hypokalemia onset in teens and younger should be investigated for potential genetic abnormalities, i.e. Gitelman syndrome, Bartter syndrome, and Liddle syndrome [97]. Hypokalemia can often be associated with hypomagnesemia. Hypomagnesium lifts the magnesium-mediated inhibition to the apical K^+ (renal outer medullary

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potassium, ROMK) channel, causing increased distal tubular K^+ excretion [98]. Failure to correct hypomagnesemia renders hypokalemia refractory to treatment.

Pathophysiology

Potassium Regulation

Potassium (K^+) is the dominant intracellular cation, with >98% of total body K^+ (~3500 mmol) being distributed in the intracellular compartment and <2% (~65–70 mmol) in the extracellular fluids. The sharp intracellular-to-extracellular K^+ gradient is critical to the maintenance of plasma membrane potential and normal functions of multiple tissues, especially the heart, nerves, and skeletal muscle. K^+ also participates in the regulation of cell volume and cellular pH. The kidneys are the major K^+ regularly organ. K^+ is freely filtered through glomeruli. The proximal tubules reabsorb ~65% of the filtered K^+, while the thick ascending limb of the Loop of Henle reabsorbs ~25%. The distal nephron (the distal convoluted tubule and collecting duct) is the major site of renal K^+ regulation. The distal nephron can either excrete or absorb K^+ to control K^+ balance. Major factors that increase distal nephron K^+ excretion are (i) serum K^+ elevation, (ii) distal tubular Na^+ delivery, (iii) tubular fluid flow, (iv) serum aldosterone elevation, and (v) alkalosis (HCO_3^- coupled K^+ excretion) or the presence of nonabsorbable anions [86]. Acidemia and hypokalemia stimulate proximal tubular ammonia genesis while alkalemia and hyperkalemia exert an inhibitory effect on ammoniagenesis.

Effects of Inadequate Dietary Potassium

A low or low-normal serum or plasma K^+ concentration, mostly a consequence of insufficient intake, can stimulate kidney NH_3/NH_4^+ genesis and RAAS activation, contributing to systemic inflammation, protein catabolism, development of CKD, and, in patients with preexisting CKD, promoting CKD progression [99]. Kaluretic diuretics, commonly used in hypertensive and CKD patients, can further exacerbate K^+ deficiency and its adverse effects [100]. Abundance of dietary K^+ is epidemiologically associated with a reduction in hypertension, stroke, and other cardiovascular diseases [101]. A recent metaanalysis of randomized controlled trials showed a mortality benefit of aldosterone antagonists in postmyocardial infarction patients with preserved ejection faction, supporting the notion of antiinflammation and K^+-sparing benefits [102].

Potassium has been shown to reduce vascular smooth muscle cell proliferation and migration. It also reduced neointimal formation following balloon angioplasty associated vessel injury. These effects were implied in a population-based study, showing an association of reduced proliferation of vascular smooth muscle cells and reduced monocyte adherence through the vessel walls [103]. Recently, Sun et al. [104] demonstrated a causal role of dietary K^+ in the regulation of osteogenic differentiation and calcification of vascular smooth muscle cells, both *in vitro* and in atherosclerotic animal models. Specifically, lower levels of extracellular fluid K^+ induce vascular smooth muscle cell osteogenic transformation by elevating intracellular calcium. The latter activates cyclic AMP response element-binding protein (CREB), leading to an enhanced expression of osteogenic markers, e.g. runt-related transcription factor 2, and, simultaneously, diminished smooth muscle cell markers, e.g. α-actin. Remarkably, even a slight serum K^+ reduction (mean K^+ level 3.70 ± 0.21 mEq/l) in mice could trigger a significant vessel calcification associated with elevated pulse-wave velocity, a reliable indicator of aortic stiffness. On the contrary, when K^+ levels are raised to ~4.73 mEq/l by dietary modification, signs of osteogenic differentiation are abrogated and vascular calcification prevented. Consistent with the notion of K^+ being protective to vasculature, a high ratio of urine Na^+/K^+ excretion (indicative of high Na^+ and low K^+ intake) has recently been linked to the genesis of hypertension [105].

Significant Tests

Pseudohypokalemia due to active cellular uptake of extracellular K^+ in the test-tube should be ruled out when the clinical setting is appropriate. It often occurs in samples from patients with severe leukocytosis or leukemia. Immediate separation of plasma from the whole-blood sample can minimize such occurrence. Pseudohyperkalemia due to cell lysis can occur during or after blood sampling from use of a small needle and inadequate technique. These possibilities can be ruled out by using an appropriate-sized needle and optimal technique.

Prognosis: Complications

Both hypo- and hyperkalemia across the spectrum of kidney function are associated with increased all-course and cardiovascular mortality [87]. Hypokalemia is also associated with an increased risk of developing CKD and CKD progression. In the PREVED (prospective, population-based) study involving 5215 adults (ages, 28–75 years) with a median follow-up of 10.3 years [106], CKD risk increased significantly in those with a lower urine K^+ content, reflecting a low K^+ diet. For each 21 mEq decrement of daily urine K^+ excretion, there was a 16% higher risk of developing CKD (defined as eGFR <60 ml/min/1.73 m^2 or albuminuria >30 mg/24 h or both). This is consistent with a prior

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cross-sectional study of dietary K^+ intake [107] and urine K^+ excretion on the risk of CKD development and progression [108, 109]. In dialysis patients (hemodialysis or peritoneal dialysis), hyperkalemia is a well-known risk for mortality. Recent studies have also shown a significant increase in morbidity and mortality associated with serum [K^+] reduction [110, 111].

Treatment

Treatment for hypokalemia includes correcting the underlying causes and K^+ replacement.

K^+ repletion can be achieved with oral or intravenous supplementation. Intravenous K^+ infusion is appropriate for patients with severe and symptomatic hypokalemia or without adequate gut function. Intravenous K^+ should not be given in a dextrose-containing solution because sugar can stimulate insulin secretion and potentially exacerbate hypokalemia by shifting K^+ intracellularly. A central line is preferred for K^+ infusion due to the vessel corrosive effect of K^+; the rate of K^+ infusion should generally not exceed 10 mEq/h (mmol/h). Hypokalemia can precipitate digoxin toxicity. Close monitoring and withholding digoxin may be necessary.

Hyperkalemia should also be managed in a multipronged manner. Dietary modification to limit dietary K^+ intake (<75 mmol/day) is an important part of intervention. The medication regimen should be reviewed to minimize exposure of drugs that may induce hyperkalemia. Loop and thiazide diuretics can be used to promote kaliuresis. In CKD patients, lack of diuretic use is associated with increased occurrence of hyperkalemia [78].

Patiromer is a nonabsorbable compound containing a Ca^{2+}–K^+ exchange polymer that selectively binds K^+, mainly in the colon. Its onset of action is 7 hours. Placebo-controlled clinical trials [80, 81] have demonstrated its efficacy and safety in lowering (normalizing) serum K^+ levels. It is Food and Drug Administration (FDA)-approved for the treatment of hyperkalemia in nondialysis CKD patients in a nonacute setting. Patiromer comes as a powder (in three strengths of 8.4, 16.2, and 25.2 g) with a recommended starting dose of 8.4 g daily. Dosage may be titrated up to a maximum daily dose of 25.2 g. Ingestion of patiromer should be spaced at least 3 hours away from intake of other medications due to a potential risk of drug–drug interaction. The most common known side effects are constipation and mild hypomagnesemia. There is a small study of hyperkalemic hemodialysis patients ($n = 6$) showing effective control of hyperkalemia with oral patiromer (12.6 g daily in divided doses) for 7 days [112].

Sodium zirconium cyclosilicate (ZS-9) is another nonabsorbable, insoluble crystal that traps gut K^+ in exchange for Na^+ and H^+. It has been shown to be effective in correcting hyperkalemia within 48 hours [82, 113]. The FDA has recently approved its use as an oral agent for hyperkalemia in patients with CKD. ZS-9 has an onset of action at ~1 hour and can be dosed 5 or 10 g/day in divided dosage. There has been no reported drug–drug interaction. Because of its gut Na^+ exchange, edema is a noted adverse effect. Other common side effects are constipation, nausea, and vomiting.

Management of acute and symptomatic hyperkalemia requires cardiovascular monitoring. In the presence of electrocardiogram (ECG) changes, intravenous calcium should be administered to stabilize the myocardium. Temporizing measures to shift K^+ into the cell interior are indicated, including albuterol (10 mg) inhalation and intravenous infusion of regular insulin (5–10 units) combined with dextrose. $NaHCO_3$ (oral or intravenous) can be added when there is coexistent metabolic acidosis. Definitive measures to excrete K^+ include loop diuretics and/or thiazide to promote renal excretion and hemodialysis. Given its relatively quick (1 hour) onset of K^+-lowering action, ZS-9 can also be used. Hemodialysis is the most effective and reliable treatment modality, especially in the setting of renal failure.

Medications that confer cardiovascular protection in heart failure patients, i.e. ACEIs, angiotensin receptor blockers, and mineralocorticoid blockers, could induce hyperkalemia and become a serious therapeutic barrier. Measures to lower serum [K^+] while keeping at-risk patients on these agents should be carried out, as limiting the use of these agents could portend to a higher all-cause and cardiovascular mortality [114].

Hypo- and Hypermagnesemia

[Mg^{2+}].

Definitions

Hypermagnesemia is defined as a serum Mg^{2+} concentration [Mg^{2+}] > 2.3 mg/dl (0.95 mmol/l) and hypomagnesemia has serum [Mg^{2+}] < 1.7 mg/dl (0.70 mmol/l).

Epidemiology

Both hyper- and hypomagnesemia are relatively common, with reported prevalences of ~31% and ~20%, respectively, in hospitalized patients [115]. In one study, oral intake of sevelamer carbonate as phosphate binder in patients with kidney failure receiving hemodialysis was associated with a lower risk of hypomagnesemia [116].

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Pathophysiology

Mg^{2+} is the second (after K^+) most abundant intracellular cation. It is a cofactor for numerous (>600) intracellular enzymes and has multiple functions in oxidative phosphorylation, DNA synthesis repair and replication, RNA and protein synthesis, and signaling pathways [1].

Daily Mg^{2+} intake in an adult should be ~350–450 mg (14.4–18.5 mmol). It is absorbed predominantly in the distal small intestine through a paracellular process and in the cecum and colon by a transcellular process involving TRPM6 (Transient Receptor Potential *cation channel,* subfamily M, member 6). Intestinal Mg^{2+} absorption can vary significantly from 25% to 75% depending on the Mg^{2+} intake. Notably, ~60% of the US population show insufficient dietary Mg^{2+} intake [117].

Greater than 99% of the total body Mg^{2+} is distributed in the intracellular compartment with ~1% or less distributed in the extracellular fluid. Approximately 20–30% of circulating Mg^{2+} is protein-bound (mainly to albumin). Unbound Mg^{2+} (70–80%) is freely filtered through glomeruli in the kidneys. The kidneys filter ~2400 mg (98.7 mmol) of Mg^{2+} daily. Unlike Na^+, K^+, and Ca^{2+}, the largest part of the filtered Mg^{2+} (70%) is absorbed, not in the proximal tubules (20% Mg^{2+} absorption), but in the thick ascending limb of the Loop of Henle (TALH), where claudins 16 and 19 facilitate paracellular Mg^{2+} absorption. The major driving force for Mg^{2+} absorption is the lumen-positive transepithelial voltage, generated primarily by the reabsorption of Na^+, K^+, and Cl^- in the TALH. The remaining 5–10% of filtered Mg^{2+} is reabsorbed in the distal tubule through a transcellular process involving TRPM6. When in balance, ~100 mg (4.1 mmol) of filtered Mg^{2+} is excreted in the urine daily (reviewed in [118, 119]). Causes of hypo- and hypermagnesemia are listed below [86]. Mg^{2+} repletion improves clinical symptoms. In patients with diabetes, Mg^{2+} repletion has been shown to improve insulin sensitivity [120]. Causes of pathologic states of hypo-and hypermagnesemia are shown in table 60.5.

Table 60.5 Major Causes of Hypo- and Hypermagnesemia.

	Hypomagnesemia	Hypermagnesemia
Hereditary	• Maturity onset diabetes of young (MODY) • Gitelman syndrome • Barter syndrome-type V	• Familial hypocalciuric hypercalcemia (FHH) (autosomal dominant inheritance)
Acquired	• Gut causes (malabsorption, chronic diarrhea) • Kidney causes (recovery phase of obstructive uropathy and acute tubular necrosis)	• Advanced renal failure + high Mg^{2+} intake
Hormonal deficiency	• Parathyroid hormone • Insulin • Estrogen • Vitamin D	
Medications	• Loop/thiazide diuretics • Proton pump inhibitors • Calcineurin inhibitors (cyclosporin, tacrolimus) • EGFR (epidermal growth factor receptor) antibodies (cetuximab, panitumumab, and matuzumab) • Platinum-containing agents (cisplatin, carboplatin) • Tyrosine kinase inhibitors • Aminoglycosides • Amphotericin • Patiromer • Non-Mg^{2+}-containing osmotic laxatives	Mg^{2+}-containing oral agents • Mg^{2+}-containing laxatives (milk of magnesium) • Epsom salt water • Mg^{2+}-containing antacids Intravenous Mg^{2+} infusion: • Magnesium chloride • Magnesium sulfate
Electrolyte disturbances	• Hypercalcemia • Hyperphosphatemia • Chronic metabolic acidosis	

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Table 60.6 Evidence table: magnesium disorders.

Treatment	Recommendation	Certainty of evidence	Strength of recommendation
Hypomagnesemia			
Correcting the underlying causes	We recommend control of hyperglycemia, replacement or discontinuation of Mg^{2+} wasting diuretics and proton pump inhibitors, and correction conditions that lead to Mg^{2+} loss be used to management hypomagnesemia	High	Strong
Mg^{2+}-rich diet	We recommend intake of a diet rich in dark green leafy vegetables, beans, nuts, seeds, fish, avocados, dark chocolate, etc.	Moderate	Strong
Oral Mg^{2+} salts	We recommend use of magnesium replacement alone or in combination	Moderate	Strong
Parenteral Mg^{2+} administration	Recommend intravenous magnesium replacement for symptomatic hypomagnesemia as a temporizing measure Oral magnesium salt administration is required to replace total body Mg^{2+} store	High	Strong
Hypermagnesemia			
Self-correct through urine Mg^{2+} excretion	We recommend self-correct through urine Mg^{2+} excretion for patients with adequate renal function	High	Strong
Loop diuretics	We recommend use of loop diuretics if necessary to enhance renal Mg^{2+} excretion	Moderate	Strong
Intravenous calcium	We suggest intravenous calcium be used for symptomatic hypermagnesemia to temporarily stabilize the myocardium	Moderate	Medium
Dialysis	We recommend dialysis be used as the most effective and definitive treatment of hypermagnesemia, especially for patients with compromised kidney function	Strong	High

Diagnostic Tests

Because albumin binds ~15–20% of circulating Mg [121], alterations in serum albumin concentration could, to a degree, alter the serum [Mg^{2+}]. As serum Mg represents <1% of the total body Mg^{2+}, the [Mg^{2+}] may not reflect the intracellular and tissue Mg^{2+} content. However, when chronic, serum Mg^{2+} could be in equilibration with the tissue Mg^{2+}, and a reduced serum [Mg^{2+}] thus signifies a significant intracellular and tissue Mg^{2+} depletion. Measuring red blood cell Mg^{2+} has not been reliably reflective of total body Mg^{2+} status. More precise methods are Mg^{2+} tolerance test and Mg^{2+} loading study [121–123]. These methods, however, are time-consuming and impractical in the setting of hospital admission.

Prognosis: Complications

Both hypo- and hypermagnesemia adversely impact patient outcomes, including increased mortality and duration of hospital stay [115, 124–126].

Treatment

Treatment of dysmagnesemia involves eliminating the underlying causes if possible and normalizing blood and tissue Mg^{2+}. For severe symptomatic hypomagnesemia, parenteral Mg^{2+} administration is indicated. Oral Mg^{2+} preparations in divided doses daily, however, are the only effective method for total body Mg^{2+} repletion. Hypermagnesemia in patients with adequate renal function is typically transient and can mostly self-correct with urine Mg^{2+} excretion. If necessary, Mg^{2+} losing diuretics (loop and thiazide) can be used to enhance renal Mg^{2+} excretion. In patients with advanced renal failure and symptomatic hypermagnesemia, intravenous calcium should be considered to stabilize the myocardium. Dialysis in such settings is the most effective and definitive treatment of hypermagnesemia. Table 60.6 summarizes the quality of evidence and strength of recommendations for the various components of the management of magnesium disorders.

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61

Metabolic Evaluation and Prevention of Kidney Stone Disease

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Introduction

The field of kidney stone prevention is still in its infancy, with a relative paucity of high-grade data suitable for inclusion in this textbook which promotes evidence-based medicine (Table 61.1). Numerous studies regarding treatment and patient outcomes are underway and robust, evidence-based data should become increasingly available [2]. Insights from genetics, understanding of microbiota, and an appreciation of the "exposome," the accumulation of environmental exposures during a lifetime, are contributing to our understanding of kidney stone disease as a chronic metabolic condition marked by acute episodes [2].

Kidney stones are becoming more common. The overall prevalence of kidney stones has increased from affecting 3.8% of the population in 1976–1980 to 8.8% of the population in 2007–2010 based on National Health and Nutrition Examination Survey (NHANES) data. Non-Hispanic white men have the highest prevalence of stones, followed by Hispanic men, non-Hispanic white women, and Hispanic women. Non-Hispanic black men and women have the lowest prevalence of stones at 4.8% and 4.2%, respectively [3]. The prevalence of kidney stones increases with age: 16% of men and 7% of women over the age of 70 had passed at least one stone. The prevalence of kidney stones increases in men until the age of 65, and in women until the age of 70 [4].

Besides causing episodes of acute nephrolithiasis, stones are associated with significant morbidity, which may be attributed to shared risk factors. In a group of calcium oxalate stone formers, the prevalence of diabetes mellitus, hypertension, and increasing body mass index (BMI), all risk factors for stone disease, increases from age 18 to 69 prior to declining in those aged 70+ [5].

There is a higher risk of cardiovascular disease in women stone formers compared to nonstone formers [6]. A larger cohort study of over three million people in Alberta, Canada found a higher risk of acute myocardial infarction, higher risk of PTCA (percutaneous transluminal coronary angioplasty)/coronary artery bypass graft (CABG), and higher risk of stroke in patients with at least one kidney stone compared to patients without stones [7], particularly in young people and women. Nephrolithiasis is also associated with a twofold higher risk of end-stage renal disease (ESRD) [8]. Thus, kidney stones may be considered a risk factor for other metabolic derangements and part of a complex of other chronic diseases.

Nontraditional risk factors for stones include consideration of the patient's microbiome, the environment created by the microorganisms associated with the patient. For example, *Oxalobacter formigenes* degrades oxalate in the intestinal tract. Patients who are colonized with this organism have fewer stones and lower urinary oxalate levels [9]. Antibiotics are known to affect the prevalence of this organism in the human intestinal tract [10]. Antibiotic use is also associated with an increased risk of kidney stones [11]. Antibiotic use could affect stone risk by altering a patient's microbiome.

This chapter will focus on the evaluation of stone formers and the measures taken to prevent stone recurrence. Topics that will be covered only briefly here are the urologic aspects of stone disease, including the differential diagnosis of renal colic, the management of renal colic, and surgical management of ureteral stones.

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Table 61.1 Interventions for calcium stones.

Treatment	Recommendation	Certainty of evidence	Strength of recommendation
Thiazide diuretics	We suggest thiazide diuretic therapy may be used to reduce stone formation in people with calcium-based stones Some patients may reasonably choose not to take thiazide diuretics due to the low certainty of the available evidence	Low	Weak
Potassium citrate	We suggest potassium citrate may be used for the secondary prevention of calcium stones, although patients may reasonably choose not to due to the paucity of high-quality evidence	Very low	Weak
Fluid intake	We suggest increased fluid intake of 2.5–3 l per day to prevent stone recurrence	Moderate	Weak

Source: Based on Seliger and Kestenbaum [1].

Urologic Aspects of Stone Disease

Imaging plays an important role in the evaluation of kidney stones. A KUB (kidney, ureter and bladder x-ray) will show larger, calcium-containing stones, which are radio-opaque, but may miss small calcium-containing stones, or radiolucent uric acid or cystine stones.

Noncontrast, helical, computed tomography (CT) is considered the imaging modality of choice for the evaluation of nephrolithiasis [12]. CT has several advantages. The size of a stone can be accurately determined. Small stones and/or ureteral stones are easily visualized. Stone density, expressed in Hounsfield units (HU), may also be measured by CT. In general, HU < 500 is consistent with a uric acid stone, which may be amenable to medical dissolution therapy regardless of size [13]. Dual emission CT scanning uses X-ray beams of two frequencies to better calculate stone density and suggest stone composition. The only stones so radiolucent that they are not visualized by CT scanning are those composed of protease inhibitors used in the treatment of human immunodeficiency virus (HIV) infection [14].

Although less sensitive and specific than CT scanning, ultrasound is also helpful for the diagnosis of nephrolithiasis. Lower cost and no radiation make ultrasound a reasonable and preferable imaging modality, especially in younger patients [15]. When patients with suspected renal colic were evaluated in emergency rooms, point-of-care ultrasound approached the positive predictive value of CT scanning [15]. Patients with an initial negative ultrasound who still had signs and symptoms of renal colic then underwent CT scanning for a definitive diagnosis. This approach, however, is controversial, especially among urologists who are concerned with delayed and inaccurate diagnosis. Low-dose, noncontrast CT scans are a nice option, when available, for minimizing radiation exposure and are becoming more widely available with lower radiation exposure [16]. Other options for minimizing use of CT scans include incorporating the use of a predictive algorithm such as the STONE score to determine which patients have a high probability of an uncomplicated ureteral stone (based on male sex, acute onset of pain, nonblack race, presence of nausea, or vomiting and microscopic hematuria) [17]. Appropriately selected patients, particularly among those with a prior history, may initially be managed without CT scanning.

While facilitation of stone passage has been widely studied, the optimal prescription remains uncertain. Forced diuresis with administration of oral or intravenous fluids is not effective, probably because the affected kidney has a reduced glomerular filtration rate, with most of the fluid administered excreted by the contralateral kidney [18]. Alpha-blockers have been popular for promoting stone expulsion, but the most recent randomized controlled trials (RCTs) have not shown clear benefit of these drugs, which are thought to relax ureteral smooth muscle [19]. Despite conflicting data on benefit, recent guidelines include the use of alpha-blockers to facilitate passage of ureteric stones in a shared decision-making approach [20]. Nonsteroidal anti-inflammatory drugs may have a positive effect but have not been tested adequately.

Guidelines on Evaluation and Management of Stone Formers

Stone disease is highly recurrent. The overall risk of a second kidney stone is about 10% per year and about 50% in 5 years. However, some individuals are much more likely to develop a second stone. Table 61.2 reviews the guidelines from the American Urologic Association (AUA), which are founded on the biological reasoning that for the individual patient, management and prevention of stone recurrence can be based on the individual's unique characteristics. The overall utility of the recommended comprehensive evaluation of the patient with renal stones has not been evaluated with rigorous RCTs.

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Table 61.2 AUA guidelines for evaluation of risk of kidney stones.

- A clinician should perform a screening evaluation consisting of a detailed medical and dietary history, serum chemistries, and urinalysis on a patient with newly diagnosed kidney or ureteral stones.
- When a stone is available, clinicians should obtain a stone analysis at least once.
- Clinicians should review available imaging to quantify stone burden.
- Clinicians should perform additional metabolic testing in high-risk or interested first-time stone formers and recurrent stone formers.
- Metabolic testing should consist of one or two 24-h urine collections obtained on a random diet and analyzed at a minimum for total volume, pH, calcium, oxalate, uric acid, citrate, sodium, potassium, and creatinine.

Source: Based on Pearle et al. [21].

Evaluation of Stone Formers

Kidney stones are the result of both genetic and environmental risk factors. The hereditability of the risk of stones is high, as indicated by a near doubling of concordance for stones among monozygotic versus dizygotic twins [22]. However, the specific genes that account for this finding remain uncertain. When stone formers in a highly selected stone clinic are screened for genes known to confer risk, about 10% of pediatric patients are found to have a mutation responsible for a monogenic disorder [23].

Obesity, diabetes mellitus, and gout are increasingly common conditions and are associated with an increased risk of kidney stones [3]. Increasing prevalence of these disorders may be in part responsible for increasing prevalence of stones. Other metabolic conditions such as hyperparathyroidism increase risk of stones. Hypertension and low bone density are associated risk factors [24].

Certain occupations may also increase risk of kidney stones. For example, taxicab drivers [25] have infrequent access to rest rooms, reduce fluid intake, and urine volume, developing higher risk. Those who work in hot environments [26] or have infrequent access to fluids also have more concentrated urine and a risk for stones. Stones are more frequent at lower latitudes [27] and may increase as global warming ensues [28].

Many of these risk factors may act to promote stone formation by changing urine chemistry. Increased urinary calcium is a frequent finding in patients with calcium oxalate and calcium phosphate stones. Increased urinary oxalate promotes the former. Reduced urinary citrate excretion is frequently noted in calcium stone formers, as citrate can be thought of as a competitive antagonist for oxalate and phosphate binding to calcium. Low urine pH is seen with obesity, metabolic syndrome, and diabetes, conferring a risk of uric acid stones. The likelihood of all stones increases with higher relative supersaturations of the relevant solutes, as calculated from 24-hour urine collections [29].

The AUA guidelines recommend performing 24-hour urine collections to further evaluate patients at greater risk, though convincing evidence of the benefit of this strategy has not been produced [30]. There are reasons for and against such a diagnostic plan, with many stone specialists promoting such collections in order to select appropriate patients for various regimens. The Recurrence of Kidney Stone (ROKS) nomogram for predicting stone recurrence [31] was developed to help determine which first-time stone formers were at high risk of recurrence. Factors associated with an increased likelihood of a second stone include first stone at a young age, white race, male, and positive family history of kidney stones. Uric acid stones are most likely to recur. A stone at the renal pelvis or lower pole is associated with a higher risk of recurrence than a stone at the ureterovesicular junction (UVJ). Having any other incidentally noted stones will increase the risk of a second stone. The nomogram did not include the results of 24-hour urine collections.

Patients with multiple stones are at high risk of recurrence and should be counseled to undergo a more thorough evaluation to identify stone risk factors. Similarly, patients with stones affecting a solitary kidney should also undergo further evaluation and close follow-up. Finally, evidence of nephrocalcinosis or reduced glomerular filtration rate might suggest distal renal tubular acidosis (RTA), primary hyperparathyroidism or medullary sponge kidney, for which further evaluation is necessary.

Table 61.3 outlines some specific conditions which may increase risk for stone formation and the likely associated stone type.

Nonspecific Prevention of Stones

Drinking an adequate amount of fluid to maintain a higher urine output is the single most important preventive measure for most stones. We recommend drinking at least 2.5 l to maintain a urine volume of 2 l. This simple measure has been shown by RCT to have significant efficacy [33]. Observational studies suggest protective effects of coffee and alcohol.

Dietary intake is also a modifiable risk factor in the development of kidney stones. In observational studies, maintaining a normal BMI, eating a diet high in fruits and vegetables, and high in low fat dairy products (such as the Dietary Approaches to Stop Hypertension [DASH] diet),

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Table 61.3 Specific concerns for stone formers which increase risk for recurrent stones.

Condition	Metabolic risk	Stone type
Inflammatory bowel disease or chronic diarrhea	Hyperoxaluria Acidic urine	Calcium oxalate Uric acid
Intestinal surgery, including ileostomy or colectomy	Volume depletion, bicarbonate loss	Calcium oxalate or uric acid
Roux-en-Y, gastric bypass	Hyperoxaluria	Calcium oxalate
Sarcoidosis, primary hyperparathyroidism, immobilization, hyperthyroidism	Hypercalciuria	Calcium phosphate and calcium oxalate
Distal renal tubular acidosis	Low urine citrate, high urine pH	Calcium phosphate
Gout	High serum uric acid Overweight	Uric acid stones Calcium oxalate
Metabolic syndrome, obesity, diabetes mellitus	Low urine citrate, low urine pH	Uric acid stones, calcium oxalate stones
Renal anomaly (e.g. horse-shoe kidney)	Urine stasis	Multiple stone types
Recurrent UTI with urea-splitting organisms (e.g. *Proteus)*	High urine pH	Struvite
Medications		
Topiramate	Low urine citrate, high urine pH	Calcium phosphate
Sulfa-containing drugs	Crystallization in urine	Sulfa (medication)
Antiretroviral therapy	Crystallization in urine	Antiretrovirals (e.g. atazanavir)
Nephrocalcinosis	Hyperparathyroidism, distal RTA	Calcium phosphate or calcium oxalate
Medullary calcification with ductal ectasia (medullary sponge kidney)	Urine stasis, hypocitraturia	Calcium oxalate or calcium phosphate

Source: Based on Worcester and Coe [32].

with adequate calcium intake, and low intake of sugar-sweetened beverages were factors associated with a significantly lower risk of incident kidney stones [34]. The only positive RCT of diet for calcium stone prevention showed that a diet with restricted salt, animal protein, and oxalate content, and with an increase in calcium ingestion, was superior to a calcium-restricted diet [35]. The effect of increasing calcium intake is attributed to binding of oxalate in the intestinal lumen, limiting its absorption. In general, lower protein intake is associated with lower urinary stone risk [36], but an RCT did not show an effect [37]. Kidney stone risk may also vary by protein type, with a lower risk from dairy-based proteins and a higher risk from other animal-based proteins. Diets high in potassium or with high potassium to animal protein ratios were beneficial [38], possibly because of their greater citrate content.

Based on the findings of population-based studies and review of existing clinical trials, both the AUA [21] and the European Association of Urology (EAU) [39] recommend "normal" (not restricted) dietary calcium intake, limited sodium, and limited animal protein for patients with calcium-containing stones (Table 61.4). A recent Cochrane review also found a benefit from a normal calcium, low protein, and low-salt diet for stone patients with higher urine calcium excretion [40]. The EAU recommends general preventative measures for all stone formers, including specific dietary management based on the results of a 24-hour urine collection.

In contrast, the American College of Physicians (ACP), which limits recommendations to those backed by rigorous RCTs, only has a single guideline for dietary management of kidney stones, noting a goal of increased fluid spread throughout the day to achieve a daily urine volume of at least 2 l. Beyond stating that sodas acidified with phosphoric acid should be avoided, there were no specifics for additional dietary interventions [41]. In the absence of better RCT-derived data, we consider limiting prescriptions in this manner inappropriate.

Calcium Stones

In general, we use the appropriate medical intervention to treat the appropriate metabolic risk in calcium stone formers at high risk of recurrence. For example, thiazides would be used in recurrent stone formers or high-risk patients

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Table 61.4 AUA and EUA dietary guidelines for management of kidney stones.

AUA guidelines	General preventative measures (EAU)
All stone formers should have fluid intake that will achieve a urine volume of 2.5 l daily	Fluid intake of 2.5–3.0 l/day Circadian drinking Neutral pH beverages Goal: urine output of 2.0–2.5 l/day Goal: specific gravity <1.010
Patients with calcium stones and high urinary calcium should limit sodium intake and consume 1000–1200 mg daily of dietary calcium	Nutritional advice: balanced diet Rich in vegetables and fiber Normal calcium content (1–1.2 g/day) Limited sodium chloride (4–5 g/day) Limited animal protein 0.8–1.0 g/kg/day
Patients with calcium oxalate stones and high urinary oxalate should limit intake of oxalate-rich foods and maintain normal, or higher, calcium consumption	If a 24-h urine shows hyperoxaluria, oxalate should be restricted
Patients with calcium stones and low urinary citrate should increase intake of fruits and vegetables, and limit nondairy animal protein	If a 24-h urine shows high sodium excretion, sodium should be restricted
Patients with uric acid stones or calcium stones with high urinary uric acid should limit nondairy animal protein	If a 24-h urine shows a small urine volume, fluid intake should be increased
Patients with cystine stones should limit sodium and protein intake	If a 24-h urine shows high intake of animal protein, excess animal protein intake should be avoided
	Lifestyle advice BMI for adults: 18–25 kg/m^2 Stress limitation measures Adequate physical activity Balancing excessive fluid loss

with higher urinary calcium. Potassium citrate would be used in patients with hypocitraturia. The RCTs demonstrating benefit may be imperfect and sparse but do suggest clinically meaningful benefits with or without the use of 24-hour urine measurements to guide treatment decisions.

The current state of the art for evidence-based management of calcium-containing stones is outlined in the Table 61.5.

Table 61.5 Summary of evidence-based interventions for calcium stones.

Summary of evidence-based interventions for prevention of calcium-containing kidney stone recurrence.
Thiazide diuretics: Several RCTs show a benefit in calcium stone formers. Not all trials showed a significant benefit. Most trials involved small numbers (<100) of participants. Typical doses were higher than those commonly used to treat high blood pressure and higher than those used today for stone disease. Higher urine calcium was not required.
Potassium citrate: Five trials evaluated the effect of citrate for secondary prevention of calcium stones. Two reported a significant risk reduction. All studies had small participant numbers. Sodium citrate does not appear effective. Lower urinary citrate was not required for benefit.
Fluid: Observational data from multiple cohorts and a single RCT favor increased fluid intake to reduce stone recurrence.

Source: Based on Seliger and Kestenbaum [1].

Medications

The AUA and EAU note that high-risk stone formers are likely to benefit from medical therapy and have issued guidelines regarding appropriate treatment based on stone composition or metabolic factors. Both guidelines were based on the best available published evidence and expert opinion.

Thiazides

The AUA guidelines state that clinicians should offer thiazide diuretics to patients with high or relatively high urinary calcium and recurrent calcium stones to reduce urine calcium excretion (guideline 14, evidence strength Grade B) [21]. Appropriate doses of thiazide type diuretics include hydrochlorothiazide 25 mg twice daily, chlorthalidone 25 mg

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daily, and indapamide 2.5 mg daily. Potassium balance may be maintained with use of potassium supplements, including potassium citrate, or with spironolactone or amiloride [21]. Triamterene, which is poorly soluble, should be avoided.

The ACP guideline recommends monotherapy with a thiazide diuretic, citrate, or allopurinol to prevent recurrent stones in patients with active disease in whom increased fluid intake fails to reduce the formation of stones [41]. However, they fail to specify when these drugs are appropriate.

The EAU guidelines suggest either thiazide or potassium citrate for management of hypercalciuria, with more specific recommendations based on 24-hour urine measurements [39].

Use of thiazides may lead to hyponatremia or orthostatic hypotension, increasing fall risk. Thiazides may also cause erectile dysfunction, fatigue, and muscle symptoms [41], further limiting use. On the other hand, thiazides are associated with increased bone mineral density, a condition often associated with calcium stones.

Citrate

Potassium citrate may be used to treat hypocitraturia (e.g. as seen in distal RTA) in patients with calcium stones. Because citrate is metabolized to bicarbonate, leading to an increase in urinary pH, it can also limit the precipitation of crystals which are insoluble in a low pH environment such as uric acid and cystine. Potassium citrate or potassium bicarbonate is preferred over sodium citrate or sodium bicarbonate as the additional sodium load may lead to increasing urinary calcium.

The AUA guidelines recommend giving potassium citrate for patients with recurrent calcium stones and low or relatively low urinary citrate (guideline 15, evidence strength Grade B). It may also be appropriate in patients with normal citrate excretion when all else fails, and in those "unselected" patients who have not done 24-hour urine collections. Potassium citrate should also be offered to patients with uric acid stones (with a goal urine pH of 6.5) and cystine stones (with a goal urine pH of >7.0) [21].

The EAU recommends using alkaline citrate or sodium bicarbonate for uric acid stone formers with a urine pH < 6.0, for patients with cystine stones, and for patients with distal RTA [39]; in general, sodium should be avoided in calcium and cystine stone formers.

Potassium citrate may cause gastrointestinal symptoms like dyspepsia. Some patients have better gastrointestinal tolerance of potassium bicarbonate compared with potassium citrate. Careful monitoring is advised in patients with mild renal impairment, particularly those who are adherent to low-salt diets (which will further limit potassium excretion) or on medications which impair potassium excretion such as an angiotensin converting enzyme inhibitors, angiotensin receptor blockers, or mineralocorticoid antagonists.

Allopurinol

The AUA suggests limiting use of allopurinol as first-line therapy for management of uric acid stones [21], as most patients have low urine pH as the predominant urinary risk factor rather than hyperuricosuria. Of the four RCTs which evaluated the role of allopurinol in management of calcium oxalate stones, the only one which showed a benefit enrolled patients with hyperuricosuria and excluded those with higher urine calcium excretion [42]. Thus, patients with recurrent calcium oxalate stones with hyperuricosuria may benefit from allopurinol therapy.

Allopurinol must be used with caution, starting with low doses and increasing gradually in patients with chronic kidney disease [43]. Whether febuxostat, which is excreted by the kidneys, has the same benefit has not been evaluated.

Other Treatments for Kidney Stones

The EAU guidelines suggest use of magnesium supplements in calcium oxalate stone formers with hypomagnesuria. For patients with enteric hyperoxaluria, the result of steatorrhea, calcium supplementation (200–400 mg daily), is recommended to bind oxalate in the intestinal lumen. For some patients with primary hyperoxaluria due to primary hyperoxaluria type 1, pyridoxine is effective in reducing urinary oxalate and therefore recommended [39]. Patients with a common missense mutation may particularly benefit from pyridoxine [44].

Calcium Phosphate Stones

Young women have a higher prevalence of calcium phosphate stones. This decreases with age, as calcium oxalate becomes the predominant stone type [45]. Although calcium oxalate stones remain the most common type of stone, both men and women show an increased prevalence of uric acid and struvite stones with age. The percentage of uric acid stones shows significant increase after the age of 50. Calcium phosphate stones are also associated with hyperparathyroidism, distal RTA, and use of drugs with carbonic anhydrase activity such as topiramate.

EAU guidelines recommend evaluation for hyperparathyroidism and distal RTA (especially if the urine pH is

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elevated) in patients with calcium phosphate stones, including carbonate apatite, or brushite stones [39].

Distal RTA (type 1 RTA) is suggested by a higher urinary pH (6.5) and low urinary citrate. Complete distal RTA may be accompanied by a low or low normal serum bicarbonate and/or a low serum potassium. If the serum values are normal, an incomplete distal RTA may be diagnosed. A diagnosis of distal RTA, or incomplete RTA, may be confirmed by response to an ammonium chloride load or to a challenge with furosemide and fludrocortisone, a maneuver that maximizes urinary acidification [46]; patients with distal RTA will not be able to acidify the urine (<5.5) in response to these maneuvers. The furosemide/fludrocortisone test has a positive predictive value of 30% and a negative predictive value of 98% in incomplete RTA. The addition of fasting urine pH and serum potassium parameters improved the sensitivity of the test to 85% and specificity to 77% [47]. Using these maneuvers to make the diagnosis is probably not necessary, since citrate supplementation will be appropriate whether urinary acidification does or does not occur [48]. Hypercalciuria and osteoporosis are often present because of acidosis-induced stimulation of osteoclast activity and inhibition of renal calcium reabsorption [49].

Potassium citrate or potassium bicarbonate, at doses sufficient to titrate the daily acid load (1 mEq/kg body weight/day) are generally sufficient. A corresponding increase in the urine citrate may not be appreciated but the serum bicarbonate should improve.

Patients with primary hyperparathyroidism have multiple abnormalities that increase risk for stone formation. These include a marked increase in urinary calcium, while urinary oxalate, phosphate, and pH may also increase. In turn, this leads to a higher supersaturation for both calcium oxalate and calcium phosphate stones, even though urine volume is also increased [50]. It is important to know that patients with primary hyperparathyroidism may have predominantly calcium oxalate stones. Initial treatment for primary hyperparathyroidism consists of surgical resection.

Struvite Stones

Struvite stones are composed of magnesium ammonium phosphate. Carbonate apatite is often present in these stones as well. Urinalysis discloses high urine pH (>8.0) and classic "coffin lid" shaped crystals. Patients with recurrent upper tract infections with a urea-splitting bacterium such as *Proteus* or *Klebsiella* are at high risk of struvite stones. Women and patients with a neurogenic bladder or with a urinary diversion are at higher risk. Since stone fragments remaining in the kidneys may form a nidus for recurrent infection, the goal of surgical therapy is to completely remove all stones. For patients in whom effective surgical treatment is not possible, acetohydroxamic acid, a urease inhibitor, or antibiotic suppressive therapy may be considered [21]. Since struvite stones can occur in combination with other stone types, particularly calcium phosphate, full metabolic evaluation is still important to minimize other risk factors.

The EAU guidelines also recommend antibiotics, urinary acidification with either ammonium chloride or methionine, or acetohydroxamic acid [39].

Uric Acid Stones

Uric acid stones are most often radiolucent by plain film. They are readily identifiable by CT, as generally the HU are <500. Uric acid stones, even those that are quite large, may respond to medical dissolution therapy that consists of increasing the urine pH, generally with potassium citrate. Uric acid is insoluble and will precipitate, leading to stone formation or growth at an acid pH. The solubility increases with increasing pH. The goal is a pH above 6.5, which may require 20 mEq of potassium citrate two or three times each day. Repeat imaging after several months of dissolution therapy will help determine if treatment has been successful or if surgical intervention is needed. Since uric acid stones have an increased tendency to recur, life-long prophylactic therapy may be considered. One dose of potassium citrate at night, to achieve one daily urinary alkalinization, may be sufficient to prevent stones when none are present [51]. All patients should be counseled on following an alkali-rich (or fruit- and vegetable-rich) diet with good fluid intake. Drugs such as allopurinol or febuxostat are considered second-line therapy as the primary risk for most patients is a low urine pH rather than hyperuricosuria. These xanthine oxidase inhibitors are reserved for patients who have trouble achieving higher urine pH values, such as those with chronic diarrhea or other bowel disorders.

The EAU suggests adjusting dosing with potassium citrate depending on whether or not further uric acid stone prevention or dissolution is desired. The target pH depends on whether it is used for prevention (goal pH of 6.2–6.8) or dissolution therapy (goal pH of 6.5–7.2) [39].

Cystine Stones

Patients with cystinuria have an autosomal recessive disorder leading to defective proximal tubular reabsorption of cystine, ornithine, lysine, and arginine (COLA), and are at

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risk of forming cystine stones. Patients with autosomal recessive disease have defects in *SLC3A1*, while patients with autosomal dominant disease (with variable and incomplete penetrance) have defects in *SLC7A9* [52]. A typical presentation for a cystine stone former would be the presence of unilateral or bilateral staghorn calculi, often at a young age. Urine microscopy may show classic hexagonal crystals. Addition of cyanide-nitroprusside, a useful screening test performed by laboratories specializing in stone risk factors, will be positive, yielding a purple color.

Cystine is the oxidized homodimer of the amino acid cysteine. Cystine is relatively insoluble in urine, particularly at low pH. The goals of therapy for cystine stones include alkalinizing the urine to increase cystine solubility, reducing the concentration of cystine in the urine below the threshold for precipitation (generally about 243 mg/l or 1 mmol/l) by increasing fluid intake, and maintaining cysteine in a monomeric state [53].

The goal for cystine stones is a urine pH > 7.0. This is usually achieved with potassium citrate at a dose of 20–30 mEq two or three times daily. The urinary excretion of cystine should be measured by 24-hour urine collection, and an individualized fluid prescription should be determined to maintain the urine concentration of cystine below 243 mg/l. For example, a patient who excretes 1000 mg of cystine in a 24-hour collection should be instructed to drink at least 4 l of fluid a day.

If urinary alkalinization and increased fluid intake are not sufficient to limit further cystine stone formation then treatment with thiol-containing drugs should be considered [54]. Thiol-containing drugs reduce cystine to more soluble cysteine-drug compounds. D-penicillamine or tiopronin are typically used. Tiopronin is currently the first-line thiol for cystinuria because of lower adverse event rates. Both drugs may infrequently cause diarrhea, dysgeusia, skin rash, proteinuria, thrombocytopenia, leukopenia, and nausea, which may limit use.

Since cystine stones are caused by a genetic defect in cystine transport, life-long adherence to therapy is required. Multiple urological interventions may be required, with some risk of chronic kidney disease and end-stage kidney disease.

Summary

There are no RCTs evaluating treatment options for secondary prevention of uric acid, struvite, or cystine stones. Strategies for treatment are based on observational studies and uncontrolled case series [1]. Treatment based on chemical composition of an initial stone with therapeutic strategies aimed at lowering the supersaturation for that stone type are biologically sound but have never been adequately examined in the clinical trial setting [55].

The development of kidney stones is determined by underlying genetics, the patient's microbiome, exposures, and the existence of other comorbid conditions, including diabetes mellitus, hypertension, and obesity. [2]

Optimal management of a recurrent stone former thus requires addressing diet, fluid intake, management of known metabolic risks relevant to the type of stones produced (e.g. thiazides to lower urinary calcium in a patient with recurrent calcium oxalate and calcium phosphate stones), and addressing factors such as climate and occupation as well as management of other diseases (e.g. diabetes mellitus).

Since much treatment data in kidney stone management is based on strong associations with limited availability of robust RCTs, we counsel patients to make the simplest changes first, modifying diet and fluid intake, and achieving good control of other chronic conditions. For patients at higher risk of recurrence, including those with genetic predispositions, we engage in more intense medical management and monitoring.

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Part 11

Pediatrics

Dedication

We dedicate the Pediatric section of this book to our friend and colleague, Professor Lesley Rees, who sadly passed away on 23 May 2022. Lesley's professional life focussed on improving the lives of infants and children with chronic kidney disease (CKD). Her contributions to the fields of CKD, dialysis and nutrition have changed the way a generation of children were treated. She helped train paediatric nephrologists globally, always emphasizing the importance of clinical expertise informed by best evidence, dedication to excellence and compassion.

Professor Rees was awarded the IPNA Lifetime Achievement Award in 2016, our society's highest honour. She will be remembered for her humanity, generosity and graciousness as much as for her many brilliant academic contributions.

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62

Growth, Nutrition, and Development

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Table 62.1 is a summary of the management of growth and nutrition in children with chronic kidney disease

Introduction

Poor growth is an important complication of chronic kidney disease (CKD). Normal growth can be divided into four important phases: prenatal, infantile, childhood, and pubertal. Factors affecting growth at different phases vary, but influences on the growth process have their most dramatic effect when growth is at its fastest.

Phases of Normal Growth and the Influence of Renal Disease

The Prenatal Phase

Growth in utero is more rapid than at any other time; around 30% of final height is achieved by birth. Intrauterine growth retardation (IUGR) has a profound effect on postnatal growth: children remain small and catch-up is rare. There is an increased incidence of prematurity and IUGR in patients with renal disease [1–3]. An adverse environment in utero impairs kidney development and makes it more vulnerable to damage from a range of pathological processes [4–7].

The Infantile Phase

The extremely rapid prenatal rate of growth gradually decreases from >25 cm/year at birth to an average of 18 cm/year at age 1 year and 10 cm/year at age 2. Half of adult height is achieved by the age of 2 years. This phase is highly dependent on nutrition: 170 kcal/day is stored in new tissue in the newborn term infant, falling to 50–60 kcal/day at 6 months, 30–40 kcal/day by 1 year, and 20–30 kcal/day by age 2 years. Maintenance of normal growth is extremely difficult in the young child with CKD: poor feeding and vomiting are common and urological complications, the commonest cause of CKD in infancy, may result in sepsis, further aggravating the feeding problems or necessitating investigation and treatments with associated periods of fasting [1, 8–14].

The Childhood Phase

Growth during this phase becomes more dependent on the growth hormone (GH)–insulin-like growth factor-1(IGF-1) axis. GH is secreted in pulses, particularly at night, and this is important for its actions. Growth rate decelerates throughout childhood and will continue to do so until the onset of sex hormone production. Continuing slowing of growth in association with lack of development of secondary sexual characteristics (prepubertal deceleration) often causes concern and is a particular problem in children who have been on long-term steroid therapy [15, 16]. Growth will not resume until the onset of puberty.

The Phase of Puberty

Acceleration of growth during puberty is dependent upon the coordination of GH and sex steroid production, which together with nutrition and general health modify the genetic growth potential. Rising sex steroid concentrations stimulate GH production by increasing the amplitude of GH secretory pulses. Together they have an anabolic effect

† deceased

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Table 62.1 Management of growth and nutrition in children with chronic kidney disease

Treatment	Recommendation	Certainty of evidence	Strength of recommendation
rhGH	We recommend the use of rhGH in children with CKD 3–5 of all ages if there is still growth potential, if they have a HtSDS <3rd centile and a Ht velocity SDS <25th centile, and all other potential causes have been treated	Moderate	Moderate
rhGH dose	We recommend 45–50 μg/kg or 1.4 mg/m^2 daily	Moderate	Moderate
Gastrostomy feeding at <2 years of age	We recommend gastrostomy feeding in infants who are not gaining appropriate weight. Benefit of improved/stable growth exceeds reported harms.	Moderate	Strong
Gastrostomy feeding at >2 years of age	We recommend the use of enteral feeding if there is poor nutritional intake with low serum albumin	Very low	Weak
EAA supplements	We are unable to recommend EAA supplements as they are of uncertain benefit. There is no evidence on harms.	Very low	Weak
Amino acid PD solutions	We are unable to recommend amino acid PD solutions as there is no demonstrated benefit. There is no evidence of harms.	Very low	Weak
Intradialytic parenteral nutrition	Uncertain benefit. There is no evidence of harms.	Very low	Weak
Increase in dialysis adequacy	We recommend the use of intensified hemodialysis. No harms reported. No evidence to recommend increasing *Kt/V* in peritoneal dialysis.	Very low	Moderate
Alternate-day steroids	We recommend the use of alternate-day steroids in selected patients. No increase in harms.	Weak	Moderate
Steroid withdrawal or a no-steroid regimen post-transplant	We recommend steroid withdrawal post-transplant in selected patients no increase in harms.	Weak	Moderate

CKD, chronic kidney disease; EAA, essential amino acid; PD peritoneal dialysis; rhGH, recombinant human growth hormone.
GRADE assessment of the certainty of the evidence [9]: High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different* is low. Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different* is moderate. Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different* is high. Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different* is very high. **Substantially different = a large enough difference that it might affect decision-making*.

on muscle mass, bone mineralization, and body proportions. Rates of growth may reach as high as 12 cm/year. The pubertal growth spurt will not take place until the appearance of secondary sexual characteristics. In girls it occurs early, soon after the onset of breast development; in boys it occurs later, after the onset of penile and pubic hair development, and not until the testes have grown to 10–12 ml. It is therefore impossible to interpret growth rates without knowledge of the corresponding pubertal stage. Pubertal development and growth may be affected by CKD and steroid therapy (see below) [15–18].

Definitions

Short Stature

Height standard deviation score (HtSDS) of more than 2 SD below the mean for age and sex (<2.5th centile).

Poor Longitudinal Growth

Ht velocity SDS > 1 SD below the mean.

Malnutrition

Inadequate intake of nutrients resulting in weight loss associated with protective metabolic responses: a decreased basic metabolic rate and preservation of lean body mass at the expense of fat mass.

Protein Energy Wasting

In protein energy wasting (PEW) appetite is decreased and there is an increase in the metabolism of fat and lean body mass.

Lean tissues are wasted preferentially to fat stores. Cachexia is the term used when PEW is severe.

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Table 62.2 The differences between malnutrition and protein energy wasting (PEW)

Malnutrition	Protein energy wasting
Inadequate intake of nutrients	Inadequate intake only partially responsible
Body fat is decreased	Normal or increased fat mass
Lean body mass is initially preserved; loss of muscle mass occurs later	Loss of lean body mass
Low resting energy expenditure	High resting energy expenditure
Can be reversed with dietary intake	Inadequate response to dietary intake

The differences between malnutrition and PEW are shown in Table 62.2 [19].

Obesity

Body mass index (BMI, weight [kilograms] divided by the square of height [meters]) is used as a measure of body fat and centile charts for children are available for age and sex.

Weight category	BMI percentile range
Underweight	<5th
Normal weight	5th to <85th
Overweight	85th to <95th
Obese	≥95th

Epidemiology of Growth Disorders in CKD

Growth in children with CKD is principally influenced by age of onset and CKD stage, i.e. those in the infantile phase of growth and those on dialysis are the worst affected. The problem is of variable severity around the world, with extremes of mean HtSDS per country ranging from −1.4 to −3.5, presumably affected by local policies on CKD management and financial resources [20]. However, overall nowhere is the mean HtSDS normal.

The effect of age has been clearly shown by the United States Renal Data System (USRDS) registry: in 2015 the percentage of incident end-stage renal disease (ESRD) patients with short stature was highest in the youngest patients, at 52.7% in the 0–4 age group, 33% in the 5–9 age group, 29.4% in the 10–13 age group, and 23.8% in the 14–17 age group [21].

The effect of CKD stage has also been recently shown by the Chronic Kidney Disease in Children Study (CKiD), a US registry of children with a glomerular filtration rate (GFR) <75 ml/min/1.73 m^2. The 2014 report identified a fall in HtSDS of 0.12–0.16 for each decline in GFR of 10 ml/min/1.73 m^2 [22]. The 2006 North American Pediatric Transplant Cooperative Study (NAPRTCS) report of a very large cohort of over 5000 children with GFRs of up to 75 ml/min/1.73 m^2, covering the 10 years between 1994 and 2004, also found a correlation between GFR and HtSDS, being −3.2, −1.9, −1.5, and −0.9 for GFR < 10, 10–25, 25–50, and > 50 ml/min/1.73 m^2, respectively [23].

There is evidence that the situation has improved since two decades ago, particularly in well-resourced areas, for example in Germany the overall mean HtSDS in children on renal replacement therapy (RRT) has increased over the past 20 years from −3.0 SD to −1.8 SD. However, in the last decade the situation seems to have stabilized, with no further demonstrable improvement [24].

Effect on each Phase of Growth in Children with Conservatively Managed CKD

Prenatal Phase

Prematurity, low birth weight, and a requirement for neonatal intensive care are common, and along with these go all the associated difficulties that are known to influence growth [1–3]. Even normal infants who are growth retarded at birth frequently do not achieve catch-up growth and this has also been shown to be true for such infants with CKD [3].

Infantile Phase

Many infants are already growth retarded by the time they are first seen in a pediatric nephrology service, with losses as high as −1.68 SD from birth (−5 SD/year) [25]. HtSDS is below the normal range in most studies [1, 8–14]. Approximately one-third of the fall in HtSDS occurs during fetal life and one-third during the first 3 months of life, accompanied by a similar fall in head circumference [8, 9, 26]. Interestingly, infants who grew well continued with catch-up in early childhood [12, 25]. As well as IUGR, a proportion of infants has comorbidity and associated syndromes which may in themselves affect growth. Although half of those with GFR < 35 ml/min/1.73 m^2 showed catch-up growth, many that grew poorly had IUGR [1].

Childhood phase

By this phase many patients with CKD from infancy are growth retarded; growth parallels the centiles but without catch-up [8, 9, 25] or may fall progressively. HtSDS fell from

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−1.6 to −2.1 over 3.5 ± 3.3 years in 22 patients aged <14 years with a GFR of 32.6 ± 24.8 ml/min/1.73 m^2 [27]. However, this is not the case in all studies. Other studies have shown an improvement: +0.3 SD over 2 years in 99 children with a median GFR of 22 ml/min/1.73 m^2 and HtSDS of −1.73 [28]; a smaller study had similar findings [29]. Growth is improving over the decades: of 799 children (median age 11.0 years) participating in the CKiD (a US registry of children with a GFR < 75 ml/min/1.73 m^2) the median HtSDS was −0.55 [22], whereas in 1996 it was −1.5 in 1725 patients, −1.4 (one-third > −1.88) in 1998 with 3863 patients, and −1.4 in 2001 with 4666 patients aged <20 years and GFR < 75 ml/min/1.73 m^2 [23]. One-third of patients were below the third centile for height in the NAPRTCS 2006 study, whereas in 2014 this percentage was only 12%.

Pubertal Phase

This phase of rapid growth is another period when loss of height potential can occur. Early studies demonstrated that puberty was delayed by approximately 2.5 years in both sexes, with an irreversible decline in HtSDS [30]. However, others report normal pubertal progression and growth [24, 25, 26, 28, 31, 32]. This problem seems to be much less common now, with reports showing normal pubertal growth and development [24].

Effect on each Phase of Growth in Children on Dialysis

Many studies combine children of all ages and dialysis modality (peritoneal dialysis [PD] and haemodialysis [HD]): of 651 patients aged <18 years, 266 (41%) had a HtSDS < −1.88 [33] and 57% of over 200 on PD were growth retarded [34]. Growth has been reported to be best on CAPD compared to CCPD and HD: changes in HtSDS were −0.55, −1.69, and −1.80, respectively, over 6–12 months [35], although this effect was most noticeable in older children [36].

Infantile phase: Reports vary considerably, although overall infants either show no change in growth or a deterioration without nutritional support. No change in HtSDS was reported (−2.51 to −2.74) in 15 children <2 years treated with CAPD [37]. Deterioration in HtSDS occurred in 17 infants on PD [38] and a decline in HtSDS by −0.29 SD/year has also been reported, along with a significant improvement between the first (−0.50) and second (+0.23) years in 22 starting PD in infancy [39]. However, it appears that an early and more intensive approach to nutrition is able to maintain or even improve height SDS [1, 2, 10, 12], especially if given via gastrostomy and alongside the use of physiological pH PD solutions and recombinant human growth hormone (rhGH) [40]. The benefits of nutrition in the infantile phase have also been illustrated in a study of 101 children presenting with chronic CKD stage 4 or 5 before the age of 2 years of whom 89% were enterally fed. In this cohort, the mean height SDS improved from −2.18 at age 6 months to −0.87 at 5 years. Those without a comorbid condition achieved a mean normal adult height without the administration of rhGH [2, 12].

There are fewer studies of growth in infants on HD. In those aged 0–1 and 2–5 years at the start of HD and/or PD HtSDS was −1.99 and −2.05, respectively, falling to −2.46 and −2.32 at 1 year and −2.06 and −2.00 at 2 years [32]. There are two studies of HD, one reporting no change from −1.6 in 18 infants on HD for up to 2 years [41] and another reporting HtSDS of −3.59 in 10 infants of <10 kg, only one of whom showed any improvement in HtSDS over a mean duration of 8.5 months [42].

Growth at this phase is improving: children who started dialysis at <18 months of age between 1983 and 1995 had a height SDS of −3 compared with −1.4 in those patients who initiated HD between 1996 and 2008. This improvement appears to be due to better control of renal bone disease and the increased use of enteral feeding (including both tube and gastrostomy feeding) and rhGH [19, 40].

Childhood Phase

Reports vary from improvement from −2.13 to −1.66 in 34 patients on PD for 6 months [43] to no change over 1 year [44, 45], to a declining HtSDS from −1.71 to −1.86 at 1 year and −2.12 at 2 years in children on PD or HD aged 6–12 years [32].

Pubertal Phase

Puberty may be delayed with poor growth [46]: HtSDS fell from −1.97 to −2.36 in 94 adolescents on HD for 3 years [47] and from −1.39 to −1.59 at 1 year and −1.83 at 2 years in those on PD or HD [32]. In two recent studies, age at pubertal onset and at menarche did not differ between children on RRT and healthy children, and the serum levels of pubertal reproductive hormones were normal in the great majority of patients [24, 48].

Effect on Each Phase of Growth in Children Post Transplant

In the NAPRTCS 2014 annual report, the mean height deficits for all patients at transplantation were −1.73: −1.77 for males and −1.68 for females. Younger subjects between 2 and 5 years at transplant (−2.22) and those with prior transplants (−2.09) also had greater height deficits at the time of transplantation. Overall, mean height SDS remain relatively constant over the available follow-up period, increasing 0.1 SD every 2 years [49].

Some, but not all, studies show growth post-transplant to be superior to growth on dialysis, particularly in younger

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children [36, 50, 51]. However, comparison is difficult because as well as age at transplant, growth is influenced by pretransplant height deficit (the greater the height deficit the greater the catch-up), which is in turn influenced by diagnosis and duration of dialysis [50]. Several studies have demonstrated the importance of GFR [50, 51]: each increase in serum creatinine of 90 μmol/l (1 mg/dl) is associated with −0.17 SD [52]. The steroid regimen also affects growth (see below).

However, growth patterns differ by age at transplant, with younger subjects (less than 6 years of age) experiencing improvement in growth deficit.

Infantile Phase

Small size precludes transplantation for most children at this age. Those who do receive transplants before 2 years of age have the greatest improvement in HtSDS, with gains of +1 SD overall [53]. In the NAPRTCS 2014 report there was an increase in HtSDS of 0.26 in the first 6 months post-transplant in under 2s, with increases thereafter of 0.53 by 12 months and 0.70 by 2 years post-transplant [49].

Childhood Phase

Improvement in growth diminishes throughout childhood: 47% <6 years at transplant and 22% >6 years gained 1 SD [53]. HtSDS changed from −2.1 to −1.0 at 1 year, −1.1 at 5 years, and to −0.14 at 10 years in 54 children transplanted before age 5 years [53], from −2.0 to −1.8, −1.5, and −1.5 at 1, 2, and 5 years post-transplant in 39 children <6 years of age [54], and from −1.71 to −1.14 at 1 year and −0.55 at 5 years in 20 children <8.5 years of age [53].

In the NAPRTCS 2014 annual report, those with functioning grafts who were aged 2–5 years at transplant had similar gains in HtSDS to younger children, and a mean increase in HtSDS of 0.57 at 2 years. However, after this age (6–12 years), linear growth was stable, at about −1.9 SD. The oldest subjects also had no increase in HtSDS, the mean for which was −1.4 SD throughout [49].

Pubertal Phase

Historically, the onset of puberty has been reported to be delayed, although in accordance with bone age: in 68 patients mean chronological age and peak height velocity were 14.6 ± 1.9 years and 13.3 ± 1.9 years and 6.6 ± 1.6 cm/year and 6.5 ± 2.9 cm/year in boys and girls, respectively, menarche was achieved at 15.9 years and the duration of pubertal development was within normal limits [46]. Steroids may contribute to this delay [17]. HtSDS increased by 1.3 SD and 0.7 SD until final height (FH) in children transplanted before and after start of puberty, respectively, although pubertal height gain was reduced by 20% [50]. Ht SDS increased from −1.8 to −1.6, −1.5, −1.0, −0.7, and −0.6 over 5 years in 54 adolescents [55]. Total pubertal height gain was better in younger children, those transplanted before the onset of puberty, and those with better graft function [50, 55]. The age at onset of puberty and pubertal height gain has been positively correlated with the age at transplantation [50]. However, more recent reports are much more positive, demonstrating normal pubertal development and growth, particularly if post-transplant a steroid-free regimen is used [48]

Final Height

In all reports, conservative management is associated with a better FH than those on RRT (−1.15 vs. −2.1) [56]. For children on RRT, young age at start of dialysis and at transplant, short stature at transplant [57, 58], and graft function [57] predict FH. FH may be reached later than expected, particularly in those on long-term steroid therapy. FH was not reached until 20.2 ± 1.8 years in males and 18.8 ± 2 years in females [46, 56], with a gain of +0.87 and +0.3 SD, respectively, after the age of 18 years [56].

Final adult height is improving with time. Of 1612 patients in the European Dialysis and Transplant Association-European Renal Association (EDTA-ERA) registry who started RRT before age 19 years and reached FH between 1990 and 2011, the median FH was −1.65 (168 cm in boys and 155 cm in girls). Overall FH was within the normal range in 55% of patients. This improved to 62% between 2006 and 2011. When results were stratified for age and decade of commencement of RRT, FH increased significantly from −1.93 in those starting RRT before 1990 to −1.78 between 1990 and 1999, and to −1.61 in those starting RRT after 1999. This improvement was independent of age at the start of RRT [59].

A similar improvement with time has been shown in the United States. NAPRTCS 2014 reported the mean HtSDS of those aged >19 years to be −1.37. Twenty-five percent had HtSDS of −2.20 or worse, and 10% were over 3.22 SD below the mean. The FH improved from −1.93 in the 1987–1991 cohort, to −1.51 in the 1992–1996 cohort, − 1.06 in the 1997–2001 cohort, −0.98 in the 2002–2006 cohort and −0.89 for the most recent cohort [49].

Obesity

In accordance with the worldwide epidemic, obesity has become a problem in CKD too. Data from the International Peritoneal Dialysis Network (IPDN) from 25 countries between 1995 and 2101 showed an incidence of overweight in 32% and 12% obesity in 4474 patients under 16 years of age. When looked at according to treatment modality, 15% were overweight on HD, 12% on PD, and 43% post-transplant. Similar measures for obesity were 8%, 6%, and 17%, respectively. Overweight increased with age with a

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proportionate decrease in underweight: malnutrition was 15% in under-1s and <2% in the oldest children [60].

Patients in the NAPRTCS 2014 report gained an average of 0.83 SD in weight in the first year following transplantation and 0.90 SD by 2 years with no change over the next 5 years [49].

Obesity is associated with young age, males, short stature, duration of dialysis, and number of transplants [61, 62]. However, obesity may not be more common than in the normal population, and is strongly related to the BMI of the mother [57].

Pathophysiology of Poor Growth in CKD

Nutrition

One of the best described causes of poor growth is inadequate intake of calories and protein. This is particularly the case during the infantile phase, when growth is more rapid than at any other time and so demands relative to body size exceed any other age. The infant with CKD is often anorexic and prone to vomiting. This can also be true of older children, but effects are proportionately less [63].

PEW

PEW is associated with metabolic abnormalities (particularly acidosis) and chronic inflammation (elevated IL-1, IL-8, and TNF alpha). There is a decreased response to the anabolic hormones insulin, IGF1, and GH [19].

Sodium

A state of sodium deficiency, as occurs in tubular salt wasting disorders such as cystinosis, can lead to chronic volume contraction. This can affect growth. Salt depletion also occurs in the tubulopathy associated with CAKUT [19, 63].

PTH

Bone deformities associated with uncontrolled hyperparathyroidism (HPT) can clearly result in growth problems. Less severe HPT is also associated with poor growth due to disruption of the growth plate architecture [64].

Dialysis Adequacy

Poor clearance of toxins, fluid overload, and chronic inflammation affect the growth process [65].

GH Resistance

There is GH resistance in CKD as levels are high and IgF1 is low [66].

Steroid Therapy

Steroids adversely affect growth: they suppress pulsatile GH release from the pituitary gland mainly by reduction of pulse amplitude, interfere with GH/IGF-I receptor signaling, and modulate paracrine IGF-I synthesis and binding by IGF binding proteins [15, 17, 66].

Diagnosis/Evaluation

What to Measure to Assess Growth

Classical measures of height (Ht), weight (Wt), and head circumference along with calculation of BMI and plotting on growth charts remain the mainstay of growth assessment in children with CKD.

Available Guidelines and Systematic Reviews

Nutrition

The Kidney Disease Outcomes Quality Initiative (K/DOQI) has published guidelines for the nutritional management of children with renal disease, including methods of assessment of nutritional status, management of acid-base status, role of urea kinetic modeling, interval measurements for assessment of nutritional status, energy, protein, vitamin, and mineral intakes, dietetic input, nutritional supplements, and use of rhGH [67, 68].

CKD-MBD

There are US guidelines on diagnosis, evaluation, prevention, and treatment [69] and a Cochrane review on interventions [70].

rhGH in CKD and Post-transplant

This has been the subject of a Cochrane review [71].

Evidence for the Benefit of Interventions on Nutrition and Growth

Nutrition

Dietary supplementation, input by a dietician, and nasogastric/gastrostomy feeds are shown in Table 62.3.

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Table 62.3 Effects of dietary supplementation, specialist input by a dietician, and tube feeding on growth

Study [reference]	No. of patients	Age (years)	GFR (ml/min/1.73 m^2)	Diet	No. with nasogastric/no. with gastrostomy	Duration (months)	Growth
Improvement in growth							
Rees 1989 [1]	16	0.2–1.8	7–37	100% EAR calories for CA, 100% RDA protein for Ht age	HtSDS improved in half 10/16 were tube fed: six improved their HtSDS 60% of tube fed improved, 33% improved without tube	60	HtSDS: −2.9 (−4.1 to −1.5) At 1–2.6 years (−4.3 to −0.3) At 2–2.4 years (−4 to 0) At 3–2.0 years (−3.5 to −0.1) At 5 years (−2.2 to −0.2)
Mekahl 2010 [2]	101	0.3 (0–1.5)	<20	100% EAR calories for CA, 100% RDA protein for Ht age with protein supplement for PD	Age at start of enteral feeds 0.8 years (0–4.9) At stop 2.5 (0.1–8.7) years 66% tube fed, 37% gastrostomy, 13% Nissen	Up to 20 years	HtSDS (SD): −0.42 (2.34) at birth (n = 40), −2.07 (1.34) at 0.5 (n = 57), −1.93 (1.38) at 1 (n = 72), −1.14 (1.14) at 5 (n = 67), −1.04 (1.15) at 10 (n = 62), −1.84 (1.32) at 15 (n = 40), −1.68 (1.52) at 18 years of age (n = 32)
Ledermann 1999 [10]	26 9	0–2 2–5	29 with GFR of 6–26, six on PD	100% EAR calories for CA, 100% RDA protein for Ht age with protein supplement for PD	20/9 8 Nissen	24	WtSDS −3.1 to −1.7 at 1 year, −1.4 at 2 years, HtSDS −2.9 to −2.2 to −2.1 WtSDS −2.3 to −2 at 1 year, −1.1 at 2 years, HtSDS −2.3 to −2.0 to −2.0
Kari 2000 [12]	24 13	0.3–2	<20 PD	100% EAR calories for CA, 100% RDA protein for Ht age with protein supplement for PD	13/17 14 Nissen	≥24	HtSDS −2.34 to −1.93 HtSDS −2.17 to −1.24
Parekh 2002 [13]	17 7	<1	<65, polyuric PD	100–160 cal and 2–2.5 g protein/kg/day, 2–4 mEq sodium, 0.3–0.5 cal/ml	Both? ratio	12–24	ΔHtSDS +1.37 at 1 year, +1.82 at 2 years
Ledermann 2000 [72]	20	<1	PD	100% EAR calories for CA, 100% RDA protein for Ht age with protein supplement for PD	10/8 7 Nissen	1–59	WtSDS −1.6 at start, −0.3 at 1 year, 0.3 at 2 years HtSDS −1.8 to −1.1 to −0.8
Claris-appiani 1995 [73]	2 3	<2 >2	CRF	101–115% EAR energy, 75–113% protein	5/0	12	ΔHtSDS +1.56, WtSDS +1.72
Strife 1986 [74]	3	1.7–3.0	20–25	Starting with 50 cal/kg and increasing	3/0	11–16	WtVel from <5% to >95%, HtVel from 5–40% to 80–95%
Norman 2004 [75]	25 21	2–16	51–75 25–50	Intensive input from dietician and supplementation if EAR energy and RNI micronutrients <80%	0/1	24	All on supplements increased Ht and Wt SDS No change in HtSDS if GFR >50 HtSDS +0.1 SD, correlation between intake and ΔHtSDS if GFR < 50

(*Continued*)

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Table 62.3 (Continued)

Study [reference]	No. of patients	Age (years)	GFR (ml/min/1.73 m^2)	Diet	No. with nasogastric/no. with gastrostomy	Duration (months)	Growth
Guillot 1980 [76]	3	<3		Energy 116% EAR, protein 84%	3/0	4–37	Two improved growth, one did not
Brewer 1990 [77]	14	3 days to 3.1	PD	>90% RDA for energy for height age, 3–4 g/kg protein	13/0	3–33	Increase in HtSDS and WtSDS in 11
Sienna 2010 [78]	102	1.7 (0.9–15.6)	13.8 (3.9–61.8)		20 tube fed 82 demand fed	2.9 (0.9–11.8)	Mean BMI SD (SD) –1.22 ± 1.68 at start, 0.43 ± 0.86at removal, 0.68 ± 1.23 at 5 years Mean HtSDS 2.35 ± 1.86, −1.51 ± 0.99–1.58 ± 1.64 Mean Wt SDS −2.53 ± 1.85, −0.66 ± 0.97–0.16 ± 0.84 Controls over previous 5 years: mean BMI (SD) 0.30 ± 1.47 0.23 ± 2.62 mean HtSDS 1.04 ± 1.38, −1.17 ± 1.16 Mean Wt SDS –0.33 ± 1.48, −0.30 ± 1.97 36% of the nontube-fed and 50% of those tube-fed were overweight or obese, associated with steroid post-transplant
Hijazi 2009 [79]	52	4.4 range (0.5–18)	PD			1983–1995 $n = 23$ 1996–2008 $n = 29$	Only data: −3 ± 1.5 early era −1.4 ± 0.9 s era
Rees 2011 [40]	153	<2	PD		From diagnosis to last observation, 57 patients were fed on demand, 54 by NG and 10 by gastrostomy, 26 switched from NG to gastrostomy and six returned from NG to demand feeding		Median Δ BMISDS/year −0.54 (1.91) during demand feeding vs. +0.97 (3.43) during NG tube feeding, +1.24 (3.24) during gastrostomy feeding Median Δ HtSDS/year −1.35 (2.63) during demand feeding, −0.72 (1.59) during NG tube feeding, −0.50 (2.47) during gastrostomy feeding ($P < 0.05$ for gastrostomy vs. demand feeds)
No change in growth rate							
Shroff 2003 [41]	18	0.5–2	HD	100% EAR calories for CA, 100% RDA protein for Ht age with protein supplement for PD	9/8	0.3–26	No change in HtSDS or WtSDS

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Reed 1998 [83]	7	0.6 ± 0.7	Mean 17 (<30)	Energy based on median Wt for CA	7/0	18.6 ± 4.5	HtSDS −0.9 to −1.1, WtSDS −0.4 to −0.2
Coleman 1999 [84]	13	0.2–8.5	PD	5.9 and 3.1 dietician contacts/month	1/7	36	HtSDS from −1.2 to −1.14 and WtSDS from −1.32 to −0.73
Initial decline then normalization of growth							
Van Dyck 1999 [12]	15	<1	Creatinine >1 mg/dl in first year	1.8–2.2 g protein/kg/day (EAA supplements 20% of protein in first year), energy 120% EAR	0/0	36	Drop in first 3 months, stable after, Ht SDS −1.96, WtSDS-1.37
Abitbol 1993 [80]	12	0.25–2	<70	100% RDA energy, >140% protein	9/3	Up to 24	Ht and WtVel lowest (−2 SD) by 6 months and Ht and WtSDS by 12 months of age, then stable at −2 SD
Ramage 1999 [81]	8 7	<2.5>2.5	PD	Aiming for 100% RNI calories or greater if no response	0/12	12	Decline in HtSDS arrested No change
Deterioration in growth							
Ellis 2001 [85]	137	<5	PD/HD	Not specified	Equal at <2 years, 29%/57% at 2–5 years	Until age 6 years	WtSDS −0.77 at start, −2.04 at 1 year, HtSDS −1.75 and −2.89 without supplements, Wt SDS −1.33 and −1.70 and HtSDS −1.76 and −2.88 with supplements, respectively
Benefits of specialist input by a dietician							
Coleman 1999 [84]	781 dietetic contacts during 182 patient months	7.7 years (range, 0.2–8.5)	PD	Children <5 years of age, 5.9 (1.9) contacts/ patient/month vs. 3.1 (1.6) in children >5 years of age	82% of contacts were with children receiving nutritional support via a button		Mean Ht and WtSDS were −1.2 and −1.32 at the start, and at the end were −1.14 and −0. 73, BMI SDS from −0.91 to 0.17
Norman 1998 [82]	2 11.8 dietetic contacts/month pre-dialysis, 8.4 during the first year on PD, 4.3 during the second year	0.25	PD		Both gastrostomy	2	HtSDS increased from −1.66 to −0.17 and 0.67–0.78, WtSDS from −1.26 to −0.43 and 0.31–1.75

CA, chronological age; EAR, estimated average requirement; Ht, height; RDA, recommended dietary allowance; RNI, recommended nutrient intake; Vel, velocity;Wt, weight.

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The benefits of supplemental feeds in CKD and dialysis have been studied using case and cohort series (1, 2, 10–13, 42, 44, 75–87; Table 62.3). All but two concentrate on children <2 years of age, who might be expected to benefit most from intensive nutrition. In 14 studies there is an improvement in HtSDS [1, 2, 10–13, 40, 72–79], in three there is an initial decline followed by normalization of growth [11, 80, 81], in three there is no change [41, 83, 84], and in one there is a decline in HtSDS [85]. Six studies include older children; of these three show an improvement in growth [10, 73, 75], two show no change [81, 84], and one shows a decline in HtSDS [85]. At least the normal age-related requirements for energy and protein seem to be needed for growth improvement, with an increased protein allowance for children on PD and a smaller supplement for those on HD to allow for losses in dialysate. The intensity of input required and advantage of input from a dietician has been specifically demonstrated in two studies [81, 82], but it is likely that all studies could not have been achieved without dietetic input. Administration of supplements was by nasogastric tube or gastrostomy in all but one study; complications are not specified, but are principally in children on PD. Post-gastrostomy there is an initial post-surgical peritonitis risk but thereafter there is no increased risk [86]. There is, however, an increased incidence of exit site infection and catheter removal from infection when the gastrostomy is inserted after PD has started, a risk that may be reduced if open rather than percutaneous surgery is used. Paraoesophageal hernias have been reported [86, 87]. Successful track closure on removal and normal feeding post-transplant are the usual outcomes [88, 89].

Essential Amino Acid Supplements

Serum essential amino acids (EAAs) may be low in CKD, particularly during PD [90] (Table 62.4). It has been suggested that a low protein diet supplemented with EAAs might ensure adequate intake and reduce protein toxicity, thereby benefiting growth. The small cohort studies available are inconclusive [91–94].

Amino Acid Containing Peritoneal Dialysis Solutions

Excessive glucose absorption and dialysate amino acid and protein losses contribute to malnutrition during PD. It has therefore been suggested that using an amino acid dialysate might both decrease glucose load and replace amino acid losses (Table 62.5). However, although amino acids are absorbed in proportion to the concentration difference between dialysate and plasma [95, 96], there is no evidence for long-term nutritional benefit [97]. In addition, such solutions are more expensive than standard ones. There are no disadvantages compared with glucose as equal amounts of urea and creatinine are removed and normoglycemia is maintained although ultrafiltration is variable [98, 99, 101]. It may be that using a combination of glucose and amino acid solutions increases protein synthesis [100]. There were no reported adverse effects.

Intradialytic Parenteral Nutrition

Papers describing the effects of intradialytic parenteral nutrition on growth are summarized in Table 62.6. Losses of amino acids occur into the dialysate during HD depending on their plasma concentrations and molecular weights. Body weight but not serum albumin improved and there were no reported complications, but numbers are very small [102–105].

Dialysis Adequacy

Papers describing the effects of dialysis adequacy on growth are shown in Table 62.7. Increasing dialysis dose might be expected to benefit appetite, nutrition, and growth, and

Table 62.4 EAA supplements and growth

Study [reference]	No. of patients	GFR (ml/min/1.73 m^2)	Diet	Duration (months)	Outcome
Jones 1980 [91]	7	Severe CKF	Protein RDA for Ht age, half as EAAs	6–8	Improved nitrogen balance but no increase in HtSDS
Jureidini 1990 [92]	10	Severe CKF	Low protein and EAAs	36	Increase in Ht and WtVel
Mir 2005 [93]	20	<50	0.6 g/kg protein and ketoacids	30	HtSDS from −1.93 to −1.37
Zachwieja 1994 [94]	10	HD	AAs 0.25 g/kg body weight i.v. with dialysis	2 of 3	No improvement in plasma amino acids

Ht, height; i.v., intravenous; RDA, recommended dietary allowance; Vel, velocity; Wt, weight.

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Table 62.5 Amino acid-containing PD solutions and growth

Study [reference]	No. of patients	Dialysis	Dialysate	Duration	Outcome
Canepa 1990 [95]	7	CAPD	1% AA exchange compared to glucose 1.36%	1 exchange	Rise in plasma AAs proportional to amount of AA in dialysate; amount of AA absorbed 66% after 1 h, 86% after 4 and 6 h; loss of 116 ± 69 μmol/kg body Wt with glucose
Hanning 1987 [96]	8	CAPD	AA-based dialysate	1 exchange	Absorption of 70–73% of AAs peaking at 1 h and varied with concentration difference; levels at pre-exchange at end of cycle
Canepa 1991 [97]	8	CAPD	First morning exchange of 1% AA dialysate	12–18 months	No improvement in any plasma or anthropometric parameter of nutrition; plasma urea increased; plasma EAAs improved but intracellular pool did not
Qamar 1994 [98]	7	CAPD	AA or dextrose dialysate	3 months, crossover	No nutritional benefit from AA dialysis
Qamar 1999 [99]	7	CCPD	AA or dextrose dialysate	3 months, crossover	During AA, appetite, calorie, and protein intake improved and total body nitrogen increased in half of children; plasma albumin did not change; fasting AAs were comparable to baseline; plasma urea was higher
Canepa 2001 [100]	10	CCPD	3 : 1 ratio of glucose to AA	8 infusions	Glucose absorption was 33.7%, AA 55.2%; plasma AA levels high but plasma urea did not increase

AA, amino acid; CAPD, continuous ambulatory PD; CCPD, continuous cycling PD.

Table 62.6 Intradialytic parenteral nutrition and growth

Study [reference]	No. of patients	Intradialytic (HD) treatment	Outcome
Abitbol 1984 [102]	3	AAs added to dialysate in increasing concentrations	Zero flux of AA nitrogen when 22 mg/100 ml of AA additive in the dialysate; increase in plasma non-EAAs but not of EAAs
Krause 2002 [103]	4, malnourished	8.5% AA solution, 10–15% dextrose, 20% fat emulsion for 7–12 weeks	Oral intake improved; Wt did not improve during treatment, but did subsequently; albumin did not change
Goldstein 2002 [104]	3, malnourished adolescents	70% dextrose, 15% AAs, 20% lipids, 6 weeks	Wt improved but not albumin
Orellana 2005 [105]	9 with >10% Wt loss and <90th percentile of ideal body Wt	Thrice weekly for 3–22 months	In six patients, BMI and PCR increased, serum albumin did not change

AA, amino acid; EAA, essential amino acid; Wt, weight; PCR, protein catabolic rate.

indeed this is the case in some studies [106–108]. However, this has to be balanced against increasing dialysate albumin losses during PD [109] and increasing amino acid losses during HD [110]; it may be possible to overcome this with careful attention to diet. PD causes an influx of glucose which can contribute to obesity. High transporter status was associated negatively with HtSDS and positively with BMISDS in 51 children on PD. Large dialysate volumes also increase BMISDS [115]. For HD it is not clear if there is a maximum optimum dose. Studies of daily HD, which is likely to offer most benefit, are promising [116].

Residual renal function (RRF) has an important positive effect on clearance and growth. HtSDS improved from −1.78 to −1.64 over a year of PD in 12 patients with RRF, but declined from −1.37 to −1.90 in 12 patients without. Weekly Kt/V was not different, and only the native kidney Kt/V and creatinine clearance correlated with growth, suggesting that clearance obtained by PD cannot be equated

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Table 62.7 Dialysis adequacy and growth

Study [reference]	No. of patients	Age (years)	Duration (momths)	PD/HD	*Kt/V*	CrCl ml/1.73 m^2/ URR	Outcome
Holtta 2000 [106]	10 11	<5 >5	9	CCPD	3.1 3.2	59 78	Catch-up growth in 62%, better than *Kt/V* 1.7 and CrCl >40 (historical)
Marsenic 2001 [107]	15	14.5 ± 3.8	38 sessions	HD	<1.3 to >1.6	URR 85%	nPCR lowest if <1.3, no improvement when >1.6
Tom 1999 [108]	12	0.6–14	4–81	HD	>2.0 and high dietary intake	URR >85%	+0.31 SD/year, normal pubertal growth
Brem 2000 [109]	23 30	14.3 ± 3.6 10.6 ± 4.7	18	HD PD	Review, noninterventional		No association with albumin; inverse correlation with albumin, particularly if *Kt/V* > 2.75
van Hoeck 2003 [110]	8	2–12	1 week crossover of NIPD ± daytime icodextrin		*Kt/V* increased from 1.99 to 2.54	CrCl increased from 35 to 65	No change in plasma albumin or PD losses, increased AA losses but no change in plasma AAs
de Camargo 2014 [111]	24 on daily dialysis (DD) 26 on conventional HD (CHD)	DD 4.4 ± 4.6 CHD 10.8 ± 3.8	9.3 ± 3 months	All HD	DH, weekly *Kt/V* 8.8 ± 1.3 CHD 5.1 ± 0.9		33% in DD and 8% in the CHD gained 0.5 SD
Fischbach 2010 [112]	15	8	20.5 (11–39) months	Hemodiafiltration 6 days of 3 h/week	*Kt/V* > 1.4 per session		Growth velocity increased from 3.8 ± 1.1 to 14.3 ± 3.8 cm/year
Hoppe 2011 [113]	16	0.5–17	4.5	Nocturnal HD (NHD)	Increased from 1.74 to 2.15		Improved appetite. PCR increased from 1.2 to 1.5 g/kg body wt/day
Thumfart 2015 [114]	13 noctural HD (NHD) 13 PD	11.9–17.5 13.1–17.2	0.5	NHD/PD	NHD 2.7 PD 2.1		Increase in albumin of 1.7 g/l on NHD, no change on PD

CCPD, continuous cycling peritoneal dialysis; NIPD, nocturnal intermittent peritoneal dialysis; nPCR, normalized protein catabolic rate; PD, peritoneal dialysis; URR, urea reduction ratio.

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with that obtained by native kidneys [117]. Eleven of 20 patients on PD with a minimum *Kt/V* of 2.1, daily protein intake of 3.25 g/kg/day, and HtSDS of −2.3 improved their HtSDS by 0.55, while in nine it declined by −0.50. Variables affecting growth were nitrogen balance and residual *Kt/V* [118].

Reports of intensive in center hemodiafiltration and more frequent dialysis (in center or at home) have been associated with growth acceleration. The dietary intake and growth rate of children on maintenance hemodialysis significantly improves with increased duration of hemodialysis sessions, such as hemodiafiltration six times per week or nocturnal hemodialysis [112, 113]. Daily HD was also superior to conventional HD [111].

Although there are no demonstrable differences in growth between those on PD and those children who receive three times a week in-center hemodialysis, intensified regimens such as short daily HDF or slow overnight dialysis show particular promise, with attainment of centiles predicted from parental heights [65, 114].

Recombinant Human Growth Hormone

Papers describing the effects of rhGH on growth are shown in Table 62.8. The efficacy of recombinant human growth hormone (rhGH) in CKD and post-transplant has been the subject of a Cochrane review [130]. Fifteen randomized controlled trials involving 629 children were identified [119–129, 131–134]. rhGH at 28 IU/m^2/week resulted in a significant increase in HtSDS at 1 year (weighted mean difference [WMD] 0.78 SDS, 95% CI 0.52–1.04) and a significant increase in height velocity at 6 months (WMD 2.85 cm/6 months, 95% CI 2.22–3.48) and 1 year (WMD

Table 62.8 Effects of rhGH on growth versus placebo or no treatment

Study [reference]	No. of patients	Type of patients	Experimental intervention (rhGH dose)	Control intervention	Ht velocity, cm/year (SD), with 1 year of rhGH [treated (T) vs. control (C)]	ΔHtSDS[a] (SD) with 1 year of rhGH [treated (T) vs. control (C)]
Fine 1994 [119]	82	Predialysis, prepuberty	28 IU/m^2/week s.c. for 24 months	Placebo injection s.c. for 24 mos	T: 10.7 (3.1); C: 6.5 (2.6)	T: 1.01 (0.94); C: −0.08 (0.96)
Fine 2002 [120]	52	Post-transplant, pre-/early puberty	28 IU/m^2/week s.c. for 12 months	No treatment	T: 8.59 (2.46); C: 4.23 (1.92)	HtSDS, T: −2.58 (1.04); C: −2.99 (0.88)
Ghio 2002 [121]	21	Post-transplant, prepuberty	30 IU/m^2/week s.c. for 12 months	No treatment	T: 6.48 (3.44); C: 4.60 (4.46)	
Guest 1998 [122]	85	Post-transplant, pre-/early puberty	30 IU/m^2/week s.c. for 12 months	No treatment	ΔHt: 3.60 (2.29); velocity: 0.40 (2.46)	T: 0.30 (1.11); C: 0.00 (1.30)
Hokken-Koelega 1991 [123]	16	Predialysis, prepuberty	28 IU/m^2/week s.c. for 6 months	Placebo injection s.c. for 6 months	T: 5.2 (1.2); C: 1.5 (0.4) (over 6 months)	
Hokken-Koelega 1996 [124]	11	Post-transplant, pre-/early puberty	28 IU/m^2/week s.c. for 6 months	Placebo injection s.c. for 6 months	T: 1.4 (0.5–2.6); C: 0.8 (0.6–1.8) per 6 months	T: −3.0 (−7.6 to −1.2); C: −2.6 (−3.6 to −2.1) (per 6 months)
Kuizon 1998 [125]	14	Dialysis, prepuberty	28 IU/m^2/week s.c. for 6 months	No treatment	T: 6.30 (2.94); C: 3.60 (1.41)	HtSDS, T: −1.36 (0.59); C: −2.18 (1.05)
Maxwell 1998 (2 trials) [126]	22	Transplant, pre-/early puberty	28 IU/m^2/week s.c. for 12 months[2]	No treatment	Change in Ht: 4.90 (2.26); velocity: 0.00 (1.85)	T; 0.88 (1.17); C: −0.20 (0.67)
Powell 1997 [127]	69	Predialysis, prepuberty	28 IU/m/week s.c. for 12 months	No treatment		T: 0.80 (0.50); C: 0.00 (0.30)
Sanchez 2002 [128]	23	Transplant, prepuberty	28 IU/m^2/week s.c. for 12 months	No treatment	T: 8.00 (2.10); C: 4.80 (1.70)	HtSDS, T: −1.09 (1.00); C: −2.80 (1.00)
Santos 2010 [129]	14	CKD 2–5	28 IU/m^2/week s.c. for 12 months	No treatment	T 14.5 (1.5); C 9.5 (1.1)	

s.c., subcutaneous.
[a] For three studies, the HtSDS is shown, rather than the change in HtSDS.

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3.80 cm/year, 95% CI 3.20–4.39) [130]. Results were independent of pubertal stage or treatment modality (CKD, dialysis, or transplant). The frequency of reported side effects was similar for the rhGH-treated group and the controls. However, there was no further improvement in subsequent years of treatment. It is not certain whether rhGH therapy improves FH, but data from cohort studies suggests that it does [130]. The remaining five trials compared two different doses of rhGH: four trials compared 28 IU/m^2/week with 14 IU/m^2/week in CKD [131–133], dialysis [131–133], and post-transplant [132–134]. They showed a 1.34 cm/year (0.55–2.13) increase in height velocity in the group treated with 28 IU/m^2/week compared to those given 14 IU/m^2/week. However, increasing the dose to 56 IU/m^2/week showed no further benefit over 28 IU/m^2/week [133]. An updated Cochrane review in 2010 [71] identified one further RCT showing a significant benefit from the use of rhGH for 1 year even in the very young [129]. There is some evidence that rhGH may also improve FH [135].

Alternate Day Steroids and Steroid Withdrawal Post-Transplant

Papers describing the effects of steroid regimen on growth are shown in Table 62.9. Better growth occurs in children on alternate-day versus daily steroids, with no detriment to graft function [136–139]. However, there may be bias toward selection of better graft function in alternate-day treated patients [134, 138, 139].

Some have advocated no steroids or their withdrawal [141, 142]. Steroid withdrawal over 2–12 months benefited growth in six out of seven studies [143–149], but again selection bias applies. The same is true for patients managed with steroid-free immunosuppression [142, 150, 151]. A recent (2017) meta-analysis of corticosteroid use and growth post-transplant identified five RCTS in renal transplants. Steroid withdrawal and/or avoidance was associated with significantly improved growth compared with those who were on steroids without any rejection or other complications [140].

A study from Germany gives impressive data on the final height of 74 patients transplanted between 1981 and 2001 and in whom steroids were withdrawn by 4–6 months post-transplant. Mean follow-up was 8.5 years. The mean final HtSDS values were −0.5 and −1.0 in prepubertal and pubertal patients and were within the normal range (>−2 SD) in 94% and 80% of them. Age and HtSDS at transplant were independent predictors of adult height [152]. The mean final heights were 177 and 175 cm in males transplanted prepubertally and postpubertally, respectively, with similar figures of 165 and 162 cm for females. These compare favorably with previous studies [24, 50, 59, 66, 153] which vary from 148 to 158 cm for females and from 162 to 168 cm for males (second centiles 151 and 163 cm, respectively).

Deflazacort is derived from prednisolone and is said to have equivalent immunosuppressive effects with less toxicity. It has been shown to improve growth and body composition post renal transplant when used in an equivalent dose to prednisolone in four studies by the same group [154–157]. However, a blinded controlled trial over 1 year in 40 patients with SSNS showed no benefit for growth [158].

Table 62.9 Effects of alternate-day steroids post-transplantation on growth

Study [reference]	No. of patients on daily/no. on alternate-day steroids	Steroid regimen	Outcome
Broyer 1992 [136]	18/17	Randomized to daily or alternate day for 1 yr; all on alternate day in second year	First year, −0.29 SD on daily, +0.49 SD alternate day; second year, +0.29 SD and +0.52 SD
Feldhoff 1984 [137]	15/15	15 switched to alternate day matched with 15 on daily	Increase in HtVel in the second but not the first year
Kaiser 1994 [138]	24/31	31 switched to alternate day, but daily group had worse graft function and higher dose	+0.94 SD alternate-day, −0.86 SD daily
Jabs 1996 [139]	1664/337	Not known how regimen selected	HtSDS up to 24 months +0.5 SD on alternate-day and +0.1 SD on daily
Tsampalieros 2017 [140]	124 patients, 138 controls 268 patients, 262 controls	5 observational studies 5 RCTs	Compared to those on steroids Δ +0.34 SD Δ +0.18 SD

Vel, velocity.

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Effect of Height on Long-term Outcome

Malnutrition and poor growth are associated with increased morbidity and mortality. Patients <18 years of age initiating dialysis with hypoalbuminemia are at a higher risk for death: in 1723 children each fall of serum albumin by 10 g/l (1 g/dl) was associated with a 54% higher risk of death. This was independent of other potential confounding variables [159]. HtSDS < −2.5 at dialysis initiation is associated with poor school attendance, more time in hospital, and a twofold higher risk of death [160, 161]. Each decrease in HtSDS or Ht velocity by 1 SD was associated with a 14% and 12% increase in risk for death, respectively. There was a U-shaped association between BMI and death, with low and high BMIs associated with an increased risk for death [162, 163].

Conclusion

Short stature is common in children of all ages with renal disease and has an important influence on outcome. Adequate nutrition is vital, particularly in the first 2 years of life but also in older children. Feeds often need to be administered by nasogastric or gastrostomy tubes and require dietetic input for prescription adjustment. There is no evidence for any benefit from EAAs orally or as amino acis dialysate or for any benefit from IDPN. Dialysis prescription is likely to affect growth, but the ideal dose is unknown. The use of the lowest possible alternate-day steroid dose, or no steroids at all, offers the best chance of good growth post-transplant. One year of rhGH may improve growth by 4 cm/year for all treatment modalities and may improve FH. All these interventions have a very low complication rate.

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63

Bone Disease in Children with Chronic Kidney Disease

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Introduction

Abnormalities in mineral metabolism and bone structure are an almost universal finding in children with chronic kidney disease (CKD) and when left untreated may lead to significant complications including bone pain, avascular necrosis, and fractures which are similar to those seen in adults, as well as skeletal deformities resembling vitamin D deficiency rickets and most pertinently reduced growth rates, which are unique to children [1–3]. Such skeletal changes reflect disturbances in endochondral bone formation linked to longitudinal growth at the level of epiphyseal growth plate and alterations in remodeling process characterized by abnormalities of bone turnover, mineralization, and volume [2, 4]. In children with CKD, alterations in bone microarchitecture and quality and in vascular biology carry consequences that severely impact bone growth and strength, cardiovascular health, quality of life, and life span [5–10]. Thus, management of CKD-mineral and bone disorder is more challenging in children, which requires fine-tuning balance between promoting skeletal growth with optimum mineralization and preventing extraskeletal calcification with appropriate treatment.

Definition and Pathophysiology

In early stages of CKD, plasma levels of calcium (Ca) and phosphorus (P) are normal, and increased levels of the fibroblast growth factor 23 (FGF23) [11, 12] prevent hyperphosphatemia by enhancing renal phosphate excretion. FGF23 also decreases the synthesis of 1,25-dihydroxyvitamin D ($1,25(OH_2)D$) and increases the inactivation of vitamin D into 24-hydroxylated compounds [13]. FGF23 levels markedly increase as estimated glomerular filtration rate (eGFR) decreases. When renal function becomes severely impaired, phosphate levels rise. In parallel, reduced production of active vitamin D by the failing kidneys and by the inhibition of 1 alpha hydroxylase activity with FGF23 leads to hypocalcemia and hyperparathyroidism [14]. If hypocalcemia is not corrected, Ca is mobilized from the bone into the circulation via increased parathormone (PTH) [2, 15, 16]. Excess Ca and P are deposited in soft tissues, including blood vessels [17]. Alterations in mineral metabolism parameters, including calcitriol deficiency, hyperparathyroidism, hyperphosphatemia and elevations in FGF23 [2, 18], disordered bone remodeling, and cardiovascular calcifications accompanying CKD together point to a systemic disease, CKD-mineral bone disorders (MBD) [4]. Renal osteodystrophy (ROD) is one component of CKD-MBD. The historical nomenclature of ROD included categories such as osteitis fibrosa, adynamic bone, osteomalacia, and mixed uremic osteodystrophy (Figure 63.1a) [19]. Current guidelines favoring a unified classification that is based on bone turnover, mineralization, and volume (TMV) omit the categories above [4, 20] and ROD is now classified as low- or high-turnover ROD.

The predominant lesion on bone biopsy in children on dialysis is high bone turnover (in 57–61% of patients) and low turnover bone disease much less common (4% of patients) [19, 20]. In the largest pediatric bone biopsy study comprising 161 peritoneal dialysis (PD) patients, abnormal skeletal mineralization was even more common than turnover abnormalities (Figure 63.1b) [20]. In line with this, high turnover bone disease was seen in 29% of children with CKD stage 4, but was not seen in children with stage 2 disease, while mineralization abnormalities occurred in 42% of children with stage 2 CKD, in 80% of children with stage 4 CKD, and in over 90% of CKD stage 5D patients (Figure 63.1c) [12].

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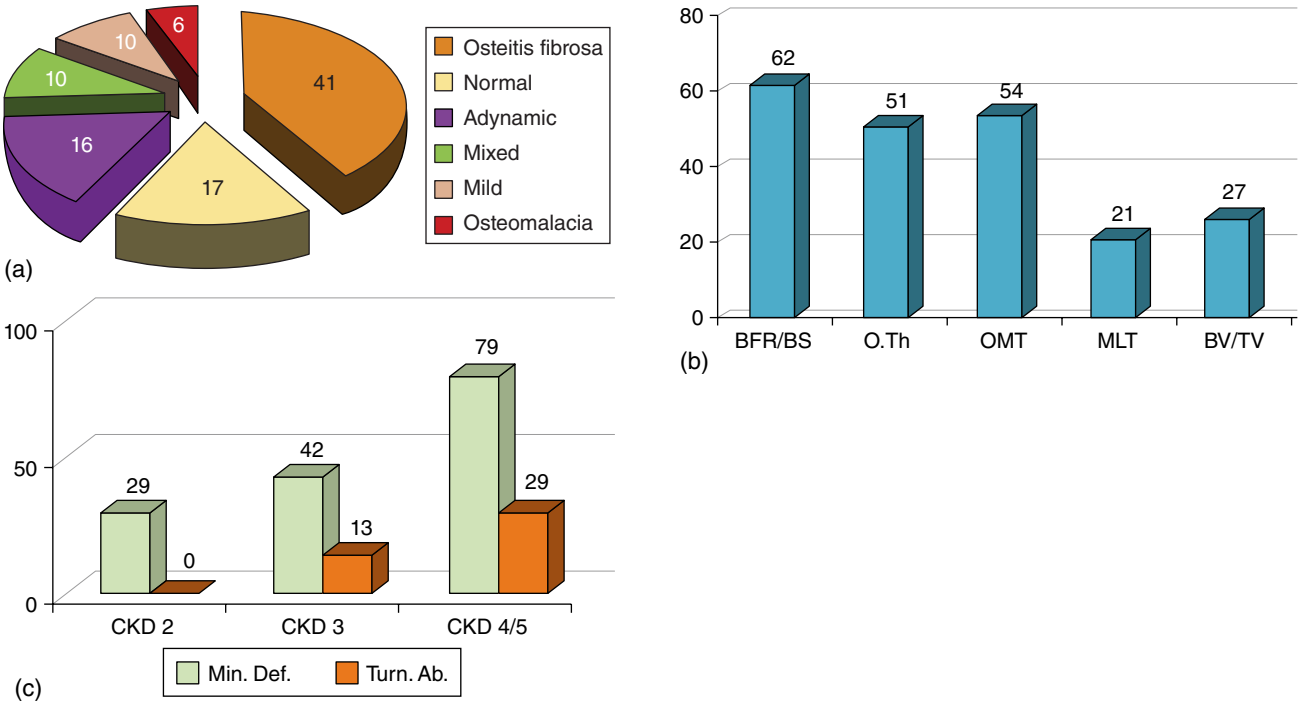

Figure 63.1 (a) Prevalence of histological types of renal osteodystrophy in children with CKD stages 5/5D. *Source:* Based on KDIGO [19]. (b) Abnormal bone histomorphometry parameters in children on PD (% cases). *Source:* Bakkaloglu et al. [20]. (c) Mineralization and turnover abnormalities in CKD 2–5 patients (% cases). *Source:* Based on Wesseling-Perry [12]. ROD, renal osteodystrophy; CKD, chronic kidney disease; D, dialysis; PD, peritoneal dialysis; BFR/BS, bone formation rate/bone surface; O.Th, osteoid thickness; OMT, osteoid maturation time; MLT, mineralization lag time; BV/TV, bone volume/tissue volume; Min. Def, mineralization defect; Turn. Ab, turnover abnormalities.

In contrast, mineralization defect was observed in only 3% of more than 600 adults on dialysis [21]. Due to modeling process and endochondral bone formation in the growing skeleton, there is a high demand for Ca to maintain bone mineral acquisition in children, including those with CKD. If this requirement is not met, mineralization defects become evident even in the early stages of CKD despite normal serum levels of Ca and P, and normal bone formation rate [12]. As such, in children undergoing PD, for any given level of bone turnover, high, normal or low, levels of PTH were higher and serum Ca values were lower in those with a concomitant mineralization defect [20]. Furthermore, lower serum Ca level was associated with lower cortical volumetric bone mineral density (BMD) and increased fracture risk in children with CKD [7, 8]. These data highlighted the importance of sufficient Ca for skeletal health during growth in CKD.

Clinical Findings

Growth Failure, Bone Deformities, and Fracture Risk

Childhood and adolescence are crucial times for the development of a healthy skeletal system. Unlike adults, skeletal growth occurs by processes of bone modeling and remodeling in children. Modeling, defined as simultaneous bone formation and resorption on different bone surfaces, is the basis of the large increase in bone size during growth. Remodeling, in which formation and resorption occur sequentially at the same location because of local coupling, allows for maintenance and repair of the skeleton [2]. Longitudinal growth is driven by the growth plate, whereas the periosteum drives bone growth in width by appositional modeling. During puberty and late adolescence, endosteal apposition and trabecular thickening provide maximum skeletal mass and strength, and therefore the growing skeleton is particularly vulnerable to the effects of CKD-MBD [2, 22]. Despite the traditional emphasis on bone turnover, significant abnormalities in skeletal mineralization have also been observed in patients with CKD and dialysis [12, 20]. Clinical implications of defective mineralization in patients with CKD remain to be further elucidated. These lesions persist despite adequate suppression of secondary hyperparathyroidism and may contribute to increased fracture rates, bone deformities, and growth retardation [7, 8, 22–24].

Growth failure: Approximately 40% of children with end-stage kidney disease (ESKD) have a reduced final height

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Table 63.1 Treatment for chronic kidney disease mineral and bone disorder in children [115].

Treatment	Recommendation	Certainty of evidence	Strength of recommendation
Phosphate binder therapy	We suggest that phosphate lowering therapy be used to lower age-appropriate serum phosphorus levels in children with CKD. The choice of phosphate-lowering treatment based on age-appropriate serum calcium levels is emphasized. Calcium-based binders are suggested as first line based on very low certainty that low calcium levels are associated with mineralization defect and fracture risk in observational studies. If serum calcium measurements show a trend toward the age-adjusted upper limit of normal sevelamer may be considered.	*Moderate (lowering phosphate levels)* *Low* (hypercalcemia) *Very low* (mineralization, fracture risk)	Weak [56, 70]
Vitamin D	We suggest using vitamin D compounds in children with CKD stages 3a–5D who have persistently increased serum PTH concentrations above the CKD-specific target range. We suggest that oral calcitriol, 1α-hydroxyvitamin D, and paricalcitol are safe and well tolerated in children with CKD stages 3a–5D.	Moderate (decrease PTH secretion) Low (hypercalcemic episodes) Very low (the effect on bone morphology and growth is uncertain)	Weak [56, 81]
25-hydroxy vitamin D	Serum 25(OH)D concentrations are suggested to be maintained above 75 nmol/l (>30 ng/ml) in children with CKD stages 2–5D.	Moderate (time to development of secondary hyperparathyroidism) Very low (the effects of 25(OH) D concentrations on bone) Low (the optimal target level)	Weak [86]
Calcimimetic	We suggest that cinacalcet be initiated for the treatment of secondary hyperparathyroidism in children with ESKD in whom secondary hyperparathyroidism is not adequately controlled with conventional treatment.	Moderate (PTH lowering effect) Very low (growth, bone disease)	Weak [100–102, 104]
Serum biochemical targets	We suggest an individualized approach to management based on trends in biochemical values rather than treating to specific targets.	Very low (optimal identification of turnover type by PTH and other clinically used markers)	Weak

GRADE assessment of the certainty of the evidence [115]: High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different* is low. Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different* is moderate. Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different* is high. Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different* is very high. **Substantially different = a large enough difference that it might affect decision-making*.
25(OH)D, 25-hydroxy vitamin D; CKD, chronic kidney disease; PTH, parathyroid hormone.
Source: Based on Hultcrantz [115].

(<3 percentile), and thus growth failure is a hallmark of CKD in children [25]. In a cross-sectional study of 5615 pediatric CKD patients included in the North American Pediatric Renal Trials and Collaborative Studies registry, overall 37% of subjects had short stature [26]. There was an almost linear relationship between growth failure and eGFR decrease. Growth deficit was seen in 68% of those with an eGFR of <10 ml/min/1.73 m^2 and in 22% of those with an eGFR of 50–75 ml/min/1.73 m^2 [26]. In a cohort of 249 young Dutch adults with childhood onset of ESKD, 61% had severe growth retardation and 18% were disabled by bone disease [27]. Along with the psychosocial disadvantages of growth failure, uremic children with growth failure have been demonstrated to have an increased risk of death [28]. In the updated Kidney Disease: İmproving Global Outcomes (KDIGO) guidelines, it is recommended that infants with CKD stage G2–G5D have their length measured at least quarterly, while children with CKD stage G2–G5D should be assessed for linear growth at least annually [29].

Bone deformities: Children with CKD also experience bone deformities [2 ,3] and fractures [24] (Figure 63.2).

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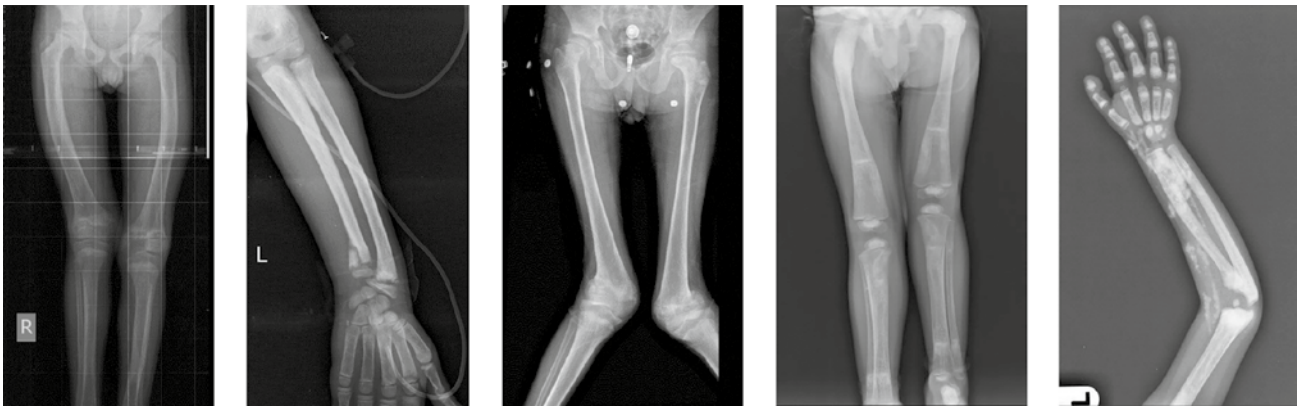

(a) (b) (c) (d) (e)

Figure 63.2 Skeletal findings of CKD-MBD: (a) coxa vara, (b) pathologic fracture, (c) genu valgum, (d) slipped capital femoral epyphysis and leg length discrepancy, (e) extensive soft tissue and vascular calcification.

Renal osteodystrophy may clinically manifest as slipped epiphyses of the femur, humerus, radius, and/or ulna, resulting not only in skeletal deformities, but also pain, abnormal gait, and/or inability to ambulate. Genu valgum, genu varum, and pes varus may also occur and, importantly, may persist despite long-term treatment with active vitamin D sterols [2, 3, 22]. In a review of 890 children on peritoneal dialysis, 9.4% had radiological signs of osteodystrophy/rickets, 5% had limb deformities, 1.4% had bone pain, and 1.5% had extraskeletal calcification [3]. Among 271 patients followed for 12 months, signs and symptoms of CKD–MBD persisted in 20 (7.4%), resolved in 32 (11.8%), and developed de novo in 17 (6.3%) [3].

Fractures: Children with CKD have a 2- to 3-fold higher gender-specific fracture risk compared to healthy children [23]. In a prospective study of 537 children with CKD (median age 11 years and mean eGFR 47 ml/min/1.73 m^2), 16% were reported to have a prior history of fracture, and over a median follow-up of 3.9 years 67 (12.5%) reported an incident fracture [23]. For fracture resistance, cortical bone is of vital importance because cortical bone represents nearly 80% of human bone mass and is the major determinant of bone strength in all individuals, including those with CKD. Prominent cortical changes of increased porosity and reduced cortical thickness occur in patients with CKD. A small adult study revealed deterioration of cortical microarchitecture contributing to bone fragility, despite predominantly normal trabecular parameters, which reinforces the importance of comprehensive cortical evaluation (not captured in the TMV system) in patients with CKD [30]. Cortical dimensions were correlated with bone strength in children [6, 7, 31]. A single-center pediatric bone biopsy study revealed a greater degree of erosion in cortical bone in CKD patients with secondary hyperparathyroidism than in those with normal or low trabecular bone turnover [32]. Progressive deficits of cortical bone have also been shown by peripheral quantitative computed tomography (pQCT) in 171 children and adolescents with CKD stages 2–5D. Importantly, greater increases in serum Ca levels were associated with greater increases in cortical BMD *Z*-scores in growing children and lower cortical BMD predicted future fracture events [7]. Therefore, in the updated KDIGO guidelines the higher Ca requirement of the growing skeleton is recognized and serum Ca levels are suggested to be maintained in the age-appropriate normal range in children and adolescents with CKD G3a–G5D [29].

Diagnostic Tests

Parathormone and Bone Turnover Markers

In early CKD, serum levels of Ca, P, and PTH are still within the normal range, while there are preceding alterations in hormonal and signaling molecules in bone such as FGF23 and sclerostin [12]. In advanced CKD, Ca, P, and PTH are routinely tested to titrate calcitriol and phosphate binder (PB) therapy. Where available ionized calcium levels should be measured [33, 34].

Abnormalities in turnover are largely driven by elevated PTH concentrations and no biomarker so far has clearly proved to be superior to PTH in predicting bone turnover in CKD [35]. However, PTH is not a bone turnover marker as it is neither involved in the process of, nor is a direct product of, bone resorption or formation. Additionally, PTH levels have proved unreliable to independently predict bone turnover, partly due to skeletal resistance to PTH and accumulation of long C-terminal fragments as well as PTH assay

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variability [2, 36]. Low bone turnover is generally associated with low or low-normal PTH levels. However, low turnover may coexist with elevated levels of PTH and high turnover may coexist with low PTH levels [36]. Due to a complete lack of evidence, current guidelines in children markedly differ with respect to the recommended PTH target levels, ranging from two to three times the upper limit of normal (ULN) in the European guideline [37] to two to nine times ULN in the KDIGO guideline [19].

For the KDIGO 2017 Update, the Work Group encouraged the continued use of PTH trends (persistently above the ULN as well as progressively rising), rather than single time-point measurements to guide therapy [29]. Parallel to this statement, in children monitoring of serum levels of Ca, PTH, and alkaline phosphatase (ALP) activity beginning in CKD stage 2 and treatment decisions based on the serial measurements of these markers are suggested [29] because it is likely that a panel of bone biomarkers will always prove superior to a single bone biomarker. PTH values <400 pg/ml plus ALP <400 IU/l provided the highest prediction of normal bone turnover and mineralization in the largest pediatric bone biopsy study [20]. However, circulating ALP consists of mostly liver and bone isoforms, so the interindividual biological variation of ALP is large, in the order of 20%. Bone-specific ALP (B-ALP) is useful in concurrent liver disease and may have the advantage of specificity over total ALP [38, 39]. A large bone biopsy study reported that intact PTH, whole PTH, and bALP levels were associated with bone turnover; however, no biomarker singly or in combination was sufficiently robust to diagnose low, normal, and high bone turnover in an individual patient [35]. Other markers of bone formation (osteocalcin and intact procollagen type 1 N-terminal propeptide [P1NP]) and resorption (C-terminal telopeptide of type 1 collagen [CTX]) do not provide optimal discrimination of turnover type and mineralization status in ROD [40]. Therefore, KDIGO 2017 guidelines encourage using trends in PTH rather than absolute "target" values to guide therapy and when trends in PTH are inconsistent a bone biopsy should be considered [29]. Further basic research is needed to elucidate the biological processes involved in modulating these biomarkers, which might lead to more targeted therapies [41].

Bone Imaging

Dual-energy X-ray Absorptiometry

Dual-energy X-ray absorptiometry (DXA) is the most widely used noninvasive technique for measuring bone mineral content and evaluating bone mass. The 2017 KDIGO guidelines suggest DXA screening in adults with CKD stage 3–5D, if results will impact management decisions [12], i.e. individualized treatment strategies according to patients' clinical, biochemical, and BMD risk factors.

In children with CKD, DXA scans have significant limitations [33, 42, 43]. Specifically, DXA scans rely on areal (g/cm^2) rather than volumetric (g/cm^3) BMD, resulting in an artificial underestimation of bone density in children with short stature. Also, DXA scans cannot distinguish between cortical and trabecular bone, which may be differentially affected in CKD; trabecular bone mass increases and cortical bone mass decreases in response to increased PTH levels [44]. Posterior–anterior DXA projection of the spine captures the largely trabecular vertebral body, as well as the superimposed cortical spinous processes. However, the lateral projection allows a distinction to be made between the vertebral body and posterior elements. Despite these limitations, there is growing evidence that DXA BMD predicts fractures in healthy children and adolescents, and those with chronic diseases [7, 23, 45]. A recent cross-sectional multicentre study in 26 patients with CKD stage 4 and 5 (median age 11.9 years) and 77 on dialysis (median age 14.0 years) showed that routinely measured serum biomarkers Ca, PTH, and ALP taken together are moderate predictors of BMD, whereas DXA is not a useful measure [46]. Prospective studies are needed in children to determine whether DXA predicts fractures and to determine whether the International Society of Clinical Densitometry (ISCD) recommendations to measure whole-body and spine BMD in children with chronic diseases are appropriate in the context of CKD [45].

Trabecular bone score (TBS) derived from a DXA spine scan is increasingly being used in stratifying fracture risk but has yet to be validated as a measure of trabecular architecture in the setting of CKD. In a recent study, relationships between TBS and measures from DXA, HR-pQCT, and histomorphometry were determined in 50 adult CKD patients. It was suggested that TBS reflected trabecular microarchitecture and cortical width measured by bone biopsy [47].

Peripheral Quantitative Computed Tomography

Newer imaging options for stratifying fracture risk include pQCT and high-resolution (HR) pQCT [48]. Peripheral QCT is a three-dimensional method that distinguishes between trabecular and cortical bone, using a low radiation dedicated extremity scanner (distal radius or tibia), and provides volumetric measures of BMD (mg/cm^3) that are not confounded by bone size [6, 7]. The feasibility, safety, and utility of pQCT in children with CKD have been demonstrated [6, 7]. However, this imaging modality is not widely available in clinical practice, is largely operator dependent,

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different protocols are used around the world, and the reference data to calculate age-, height- and sex-adjusted Z-scores for healthy people are limited [46]. pQCT BMD measurements correlate with circulating mineral metabolism factors, including PTH, in pediatric CKD patients [7]. Hyperparathyroidism is associated with significant reductions in cortical BMD and bone size, and with greater trabecular BMD in younger children [6]. The ISCD pediatric task force recommends that pQCT "can be used clinically in children where appropriate reference data and expertise are available" [49]. On the other hand, the use of bone structural parameters to identify bone dynamic parameters is controversial and doubtful because the effects of bone turnover on bone structure require about 3–6 months to be detectable on HR-pQCT imaging [40].

Micro-MRI

Micro-MRI, a nonionizing method for in vivo quantification of bone microarchitecture, is performed using readily available clinical scanners but with customized pulse sequences and coils, and sophisticated post-processing and analysis [50]. It is not limited to peripheral bone sites and can image proximal femur [51]. Wehrli et al. evaluated the role of micro-MRI in assessing bone microstructure in 17 young adults on maintenance hemodialysis, demonstrating significantly lower cortical thickness and cross-sectional area and evidence of trabecular disruption in the dialysis patients compared to controls [52].

Currently, noninvasive high-resolution imaging is confined to the research setting. Despite limitations, including lack of standardized reference data and technical parameters, imaging to peripheral sites, high costs, very few studies, and lack of robust validation against histomorphometry in pediatric CKD, this modality has the potential to fill, at least partially, the significant gap between screening of BMD using DXA and comprehensive diagnosis by bone biopsy [53].

Bone Biopsy

Currently, double-labeled tetracycline transiliac crest bone biopsy with quantitative histomorphometry is the only way to assess three key histologic descriptors of bone histology (TMV) and to accurately assess responses to therapeutic interventions [4]. In a large pediatric bone biopsy series, approximately half of the peritoneal dialysis patients had increased bone turnover and/or abnormal mineralization [20]. This classification system focuses on trabecular bone and generally excludes an assessment of cortical microarchitecture and integrity related to fracture resistance. An adult bone biopsy study on 630 hemodialysis patients reported a high prevalence of low bone turnover and abnormal cortical parameters [21]. Significant cortical loss was shown to be mediated by hyperparathyroidism and elevated turnover [54] in adults and children with CKD [32].

Using micro-CT, bone biopsy samples from patients on dialysis often show severely thinned and porous cortices due to intracortical remodeling [54]. In a recent study, trabecular and cortical bone microarchitecture were evaluated by histomorphometry and micro-CT in 16 patients with CKD stage 5 and 5D. Deterioration of cortical microarchitecture despite predominantly normal trabecular parameters reinforces the importance of comprehensive cortical evaluation in patients with CKD [30]. Evaluation of 68 pediatric bone biopsy samples by micro-CT revealed that bone volume measurements were highly correlated between bone histomorphometry and micro-CT, whereas bone formation rate did not correlate with any micro-CT determinations [55].

For the present, bone biopsy represents an important adjunct to the clinical and biochemical evaluation of patients with CKD, particularly when patients present with bone pain or unexplained fractures [1, 19, 29]. Bone biopsy studies evaluating bone biology/physiology have emphasized the critical role of bone as an endocrine organ and improved our understanding of the pathophysiology of not only ROD but also bone/kidney/vascular axes [1, 2, 4, 19, 29]. However, bone biopsy is invasive, expensive, requires approximately 3 months for results, cannot be used for rapid decision making, is not easily implemented as a disease and treatment monitoring tool, and is available at only several centers worldwide. In addition, it assumes that iliac crest remodeling is representative of systemic turnover. It is also limited by its ability to provide a measure of bone quality at a single site and a single point in time. So, even with the availability of bone biopsy data, we may find that patients do not respond predictably to treatments [40]. Thus, a true understanding of the prevalence of abnormal turnover, defective mineralization, and altered bone volume throughout the course of CKD is limited and regular analysis of biochemical indices and attention to their trends will also be required [20, 29, 36].

Treatment

The goals of CKD-MBD treatment in children are to normalize mineral metabolism, minimize progression of extraskeletal calcification, and promote normal bone turnover and normal skeletal growth without deformities. Along with dietary interventions, PBs, active and native vitamin D sterols and calcimimetic agents for selected individuals are current practice for CKD-MBD treatment [2, 18].

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The most common treatments used in children with CKD are PBs (calcium or noncalcium containing) and vitamin D sterols (calcitriol, 1α-hydroxyvitamin D, paricalcitol). Dietary measures are instituted to reduce phosphate intake while maintaining adequate calcium and vitamin D intake for healthy skeletal growth. Also calcium levels in the dialysis fluid can be manipulated to maintain normocalcemia. New agents include calcimimetic agents (cinacalcet, etelcalcetide), which control secondary hyperparathyroidism, and for medically unresponsive patients, parathyroidectomy may be required.

Guidelines for the management of CKD-MBD in children are largely opinion-based, and many of the recommendations are cautiously vague and extrapolated from data in adults. Limited pediatric data coming from randomized controlled trials (RCTs) with a limited number of patients are focused on PTH and biochemical values only instead of patient-important health-related outcome parameters like growth, bone deformities, physical activity level, fractures, and finally death. Evidence for treatments is summarized in Table 63.1.

A recent Cochrane review concluded that there is a lack of evidence to guide CKD-MBD treatment in children with CKD and on dialysis. Hyperparathyroidism is improved by all vitamin D preparations. However, no consistent differences between routes of administration, frequencies of dosing or vitamin D preparations were demonstrated. Although fewer episodes of high calcium levels occurred with sevelamer compared with calcium acetate, phosphorus values were reduced to similar extents with all PBs [56]. After this Cochrane review, there are only a few RCTs on the effects of PBs and vitamin D, and available data is summarized below.

Phosphate Binders

Since conventional dialytic modalities remove far less than the daily dietary intake of phosphorus, PBs are routinely prescribed to control hyperphosphatemia in patients with CKD. The first agents, aluminum-containing PBs, were replaced by calcium-based PBs in the 1980s because of toxicities associated with aluminum. Then the calcium- and aluminum-free PBs sevelamer and lanthanum were introduced. Now, calcium-free iron-based PBs are on the market as promising alternatives. In the International Pediatric Peritoneal Dialysis (IPPN) Registry, among 890 patients, 88.3% were using PBs and the great majority of them (68.8%) were using calcium carbonate or acetate, 7% sevelamer (mainly in the USA), 11.8% both Ca-based binders and sevelamer, and only 0.3% lanthanum [3].

The most recent Cochrane review, including 104 adult studies in 13 744 patients [57], supported previous meta-analysis [58] and concluded that in adult dialysis patients, compared to calcium-based binders, sevelamer may lower all-cause death and incur less treatment-related hypercalcemia. There were no clinically important benefits of any PB on cardiovascular death, myocardial infarction, stroke, fracture or coronary artery calcification.

Iron lowered serum phosphorus levels to the greatest extent compared with other binders [57]. In terms of tolerability, lanthanum had the highest probability of causing nausea and sevelamer increased constipation compared with calcium, lanthanum, and iron. Iron was worst for diarrhea compared to calcium and sevelamer [58]. For predialysis patients, evidence is lacking for an advantage of any PB over placebo [57], therefore in the most recent UK Renal Association guideline PBs are suggested to be reserved for advanced stage CKD patients with progressively rising or persistently elevated serum phosphate [59].

The phosphate lowering capacity of Ca-containing PB and sevelamer is comparable [57, 60, 61]. Iron-based PBs appear to be the most effective in binding phosphate [57] and lanthanum is second [61], but these binders' long-term effects on bone and cardiovascular health are not known. Based on adult studies showing that calcium-based PBs may promote ectopic calcification [62–64], restricting the dose of calcium-based PBs is proposed in the KDIGO 2017 guidelines for avoiding hypercalcemia [29]. However, controversial data are also available [57, 62]. The most recent Cochrane review concluded that in adults with CKD and dialysis, there were no clinically important benefits of any phosphate binder on coronary artery calcification, though sevelamer incurs less treatment-related hypercalcemia [57]. Baseline calcification status is a more important predictor of calcification progression than the type of P binder [65]. Therefore, a pragmatic and individualized approach to phosphate reduction toward the normal range and maintaining serum calcium below the upper limit of the reference range are suggested in adults [59].

Several studies in children on dialysis have shown an association between high phosphate levels and increased vessel thickness/stiffness and arterial calcification [66–68]. Active vitamin D sterols and PBs have also been shown to be associated with worsening of vascular calcification [65, 66]. However, the growing skeleton of children has a high demand for calcium, and low calcium levels reduce BMD and increase fracture risk [6, 7, 23]. Furthermore, a large prospective cohort revealed that use of PBs, largely calcium-based ones, was protective from fracture in pediatric CKD patients [23]. Therefore, in children with CKD G3a–G5D, maintaining serum calcium and phosphorus in the age-appropriate normal range is suggested and the

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choice of phosphate-lowering treatment based on serum calcium levels is emphasized [29]. A calcium-based PB as the first-line phosphate reduction therapy in children should be preferred. If a series of serum calcium measurements shows a trend toward the age-adjusted upper limit of normal, either combining with, or switching to, sevelamer is suggested [59].

Only three RCTs have examined phosphate-lowering therapy in children with CKD or on dialysis (Tables 63.2 and 63.3) [60, 69, 70]. The first RCT examined biochemical endpoints (decrease in serum P levels, Ca*P product level) only and showed equivalent phosphate control with calcium acetate and sevelamer hydrochloride in an 8-week cross-over trial. There was a lower rate of hypercalcemia and lower lipid levels with sevelamer [69]. In the second study, 29 children on PD were randomized to different combinations of PBs (sevelamer hydrochloride vs. calcium carbonate) and vitamin D analogues (doxercalciferol vs. calcitriol). Bone biopsies suggested that both the sevelamer and calcium carbonate-treated groups had equally reduced bone formation rate versus baseline at 8-month follow-up, and less hypercalcemia with sevelamer was also noted [60].

The most recent phase 2 study evaluated the efficacy and safety of sevelamer carbonate in 66 children with CKD (mean age 14.1 years and 77% on dialysis). Following a 2–4-week screening phase, pediatric patients with a serum phosphorus level higher than age-appropriate levels were randomized to receive either sevelamer carbonate or placebo as powder/tablets in 0.4–1.6 g doses, based on body surface area. Dose was titrated up or down based on serum P levels after the fixed dose period. Sevelamer carbonate was shown to be effective in reducing serum P levels without any significant side effects [70].

Lanthanum is a heavy metal minimally absorbed and eliminated via the hepatobiliary pathway. Despite concerns related to bone accumulation and cartilage toxicity in growing children, randomized prospective adult studies of paired bone biopsies revealed no evidence of accumulation or toxicity in patients treated with lanthanum carbonate. There is also no evidence that lanthanum carbonate is associated with adverse safety outcomes in patients with ESKD [71]. However, there are no pediatric RCTs and its use is highly limited in children [3].

Ferric citrate (FC), an iron-based PB, has been shown to improve both hyperphosphatemia and iron deficiency in adult CKD and dialysis patients [72, 73]. In line with this, a small pediatric retrospective study ($n = 11$ children on dialysis, median age 13 years, median duration 7 months, time-averaged FC dose 3.5 (1.5–8.4) tablets/day, and elemental iron 27 [10–38] mg/kg/day) showed decreased serum phosphate, improved iron parameters, and maintenance of hematocrit with FC treatment [74]. The effects of iron-based P binders on anemia and hyperphosphatemia should be studied in RCTs.

Active Vitamin D Compounds

Deficiency in $1,25(OH)_2D$ increases PTH synthesis and secretion, both directly and due to the associated hypocalcemia. According to IPPN registry, 75% of the pediatric dialysis patients were using different active vitamin D sterols, mainly calcitriol (45.6%) and alfacalcidol (25%), and only a few patients (1.3%) were using doxercalciferol or paricalcitol [3].

Calcitriol, doxercalciferol, and paricalcitol were evaluated in RCTs (Tables 63.4 and 63.5). Two RCTs showed a significant reduction in PTH with thrice-weekly intravenous calcitriol [75] and thrice-weekly intravenous paricalcitol [76] in hemodialysis patients. The only placebo-controlled randomized trial in patients with stages 3–5 CKD showed that oral paricalcitol with an initiating dose of 1 μg three times weekly in children aged 10–16 years was effective in decreasing the iPTH levels [81]. Oral thrice weekly paricalcitol has also been shown to be safe and effective in reducing PTH in children on dialysis in an open-label study [81]. A significantly increased risk of hypercalcemia was reported with intravenous calcitriol [75], but not with IV or oral paricalcitol [76, 81]. Therefore, oral paricalcitol was shown to be safe and effective not only in dialysis patients, but also in children with CKD stage 3–4 [81]. Another controlled trial demonstrated that calcitriol and doxercalciferol exhibit equal efficacy in lowering PTH levels and in controlling bone turnover [77]. Two RCTs of alfacalcidol or calcitriol versus native vitamin D in children with CKD stages 2–3 [82] and on dialysis [83] indicated a qualitative and quantitative improvement in histological indices of renal osteodystrophy with both native vitamin D and active vitamin D analogues. Studies comparing intermittent with daily oral calcitriol showed that the change in mean height SDS and the percentage fall in PTH levels in the short (8 weeks) or long term (12 months) did not differ between treatments. It has also been reported that intermittent high-dose calcitriol may adversely affect linear bone growth [84]. Available data based on a Cochrane review in 2015 including 18 studies and 576 enrolled patients concluded that vitamin D sterols are effective in reducing PTH levels in children with CKD and on dialysis, but their effects on bone and growth are uncertain due to the small number of patients and short-term follow-up in controlled trials [56]. Based on available data we suggest using vitamin D sterols, including oral calcitriol, 1α-hydroxyvitamin D, and paricalcitol, as safe, effective, and well-tolerated agents in

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Table 63.2 Randomized controlled trials of phosphate binder treatment in children.

Author (year), country	Population, gender, age (years)	Study design, duration of treatment	Intervention (I), comparator (C)	*N* (I/C)	Primary outcome(s)	Result	Certainty of the evidence (GRADE)
Pieper (2006), Europe [69]	11 on HD, 6 on PD, 1 predialysis; 62% male, 12.4 ± 4.1	Randomized open-label, crossover trial (8 weeks per arm)	Sevelamer vs. calcium acetate	40 randomized, 18 completed the trial	Serum phosphorus	• Equivalent reduction in serum phosphorus levels in sevelamer and control groups (−1.5 ± 1.6 vs. −1.7 ± 1.7 mg/dl) • Greater incidence of hypercalcemia ($P < 0.001$) with calcium acetate • Total cholesterol (−27%; $P < 0.02$) and low-density lipoprotein cholesterol (−34%; $P < 0.005$) decreased significantly with sevelamer	Moderate
Salusky (2005), USA [60]	PD patients, 62% male, 15 ± 3, 11 ± 5	2 × 2 factorial, randomized control trial (8 months)	Sevelamer hydrochloride vs. calcium carbonate and oral doxercalciferol vs. calcitriol	42 randomized, 29 completed [14, 15]	Bone histology (all patients had high turnover at baseline) Change in biochemical parameters	• Equivalent reduction in bone formation rates in sevelamer and control groups (−53 ± 11% vs. −49 ± 7%) • Greater decline in bone resorption in the calcium-treated group • Serum calcium and Ca–P product increased with calcium carbonate ($P < 0.001$) • Hypercalcemic episodes more frequent with calcium carbonate ($P < 0.01$)	Moderate/ low
Fathallah-Shayk (2018), multicenter, USA and Europe [70]	eGFR <60 ml/min/1.73 m^2 (77% on dialysis), mean age 14.1 years	Phase 2, safety and efficacy of sevelamer carbonate randomized, placebo-controlled, fixed-dose period, 2-week single-arm, open label, dose-titration period, 6 months	Sevelamer carbonate vs. placebo and in extension phase only sevelamer carbonate	101 enrolled patients (29 centers), 66 completed	Change in serum phosphorus from baseline to end of the fixed-dose period • Secondary outcome was mean change in serum phosphorus from baseline to end of DTP	• Sevelamer carbonate significantly reduced serum phosphorus from baseline levels (7.16 mg/dl) during the fixed-dose period compared to placebo (least square mean difference −0.90 mg/dl, $P = 0.001$) and during the DTP (−1.18 mg/dl, $P < 0.0001$) • The safety and tolerability were similar • Mild/moderate gastrointestinal AEs during the DTP	Moderate

AE, adverse event; Ca, calcium; DTP, dose titration period; eGFR, estimated glomerular filtration rate; HD, hemodialysis; P, phosphate; PD, peritoneal dialysis.

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Table 63.3 Summary of findings: phosphate binder therapy.

Outcome	No. of participants (no. of studies)	Absolute no. of patients affected per 1000 patients treated for 1 year (95% CI)	Relative risk (95% CI)	Certainty of the evidence (GRADE)	Conclusion
Phosphate lowering effect	113 (3 studies)	Not estimable	Not estimable	Moderate	Phosphate binders significantly lowered serum phosphorus levels
Hypercalcemia	57 (2 studies)	Not estimable	Not estimable	Moderate	Sevelamer probably leads to less frequent hypercalcemia than calcium-based binders
Bone histology	29 (1 study)	Not estimable	Not estimable	Low	Sevelamer and calcium-based phosphate binders in combination with active vitamin D sterols may reduce bone formation rates

children with CKD stages 3a–5D who have persistently increased serum PTH concentrations above the CKD-specific target range [85].

Native Vitamin D

Vitamin D deficiency is widely prevalent and often severe in children and adults with CKD. According to the most recent clinical practice recommendations, 25-hydroxyvitamin D 25(OH)D status is classified as follows: sufficiency >75 nmol/l (>30 ng/ml), insufficiency 50–75 nmol/l (20–30 ng/ml), deficiency 12–50 nmol/l (5–20 ng/ml), severe deficiency <12 nmol/l (<5 ng/ml). It is suggested that serum 25(OH)D concentrations are maintained above 75 nmol/l (>30 ng/ml) in children with CKD stages 2–5D [86]. Levels are suggested to be monitored 6–12 months apart in patients not requiring vitamin D supplementation, when deficient 3–6 monthly measurements can be suggested according to the response to therapy [86].

There are few studies in children or adults with CKD that examine the effects of 25(OH)D concentrations on bone, and the optimal target level of 25(OH)D is unclear. In the only RCT of native vitamin D therapy in children with CKD, it was shown that children on ergocalciferol who achieved 25(OH)D levels >75 nmol/l had a significantly longer time to development of secondary hyperparathyroidism (Table 63.6) compared with those on placebo [87] Other nonrandomized prospective studies in children with CKD have also shown the effect of ergocalciferol or cholecalciferol in reducing PTH levels [88, 89].

A treatment regimen guided by age and vitamin D levels for the prevention and treatment of vitamin D deficiency in children with CKD stages 2–5D is suggested. Mega-dose vitamin D therapy is not recommended. None of the studies adjust vitamin D doses for body weight or body surface area [90]. Although the "stoss regimen" (i.e. 300 000 and 600 000 IU as single mega-dose vitamin D therapy) may overcome issues of compliance, this can cause hypercalcemia without an additional benefit to the improvement of rickets [91]. Intoxication from vitamin D is largely reported from the use of very high doses of ergocalciferol or cholecalciferol over prolonged periods of time [92]. Symptomatic toxicity from vitamin D is defined as serum 25(OH)D above 250 nmol/l with hypercalcemia, hypercalciuria, and suppressed PTH, and, if prolonged, nephrocalcinosis and renal failure. Vitamin D supplementation is therefore stopped at serum 25(OH)D concentrations of 120 nmol/l (48 ng/ml) (Table 63.7) [86].

Cinacalcet

Cinacalcet is an allosteric modulator of the calcium-sensing receptor (CaSR) expressed in the parathyroid glands. It enhances the CaSR sensitivity for extracellular calcium, resulting in reduced serum PTH, Ca, and serum inorganic phosphate levels, allowing better control of secondary hyperparathyroidism and CKD-associated mineral and bone disorders (CKD-MBD). The effect of cinacalcet therapy on reducing PTH levels and on the need for parathyroidectomy in adults is clearly shown in meta-analyses [93, 94] and its use, along with calcitriol or vitamin D analogs, or a combination thereof, is included in the KDIGO guidelines [12], but there are controversial data about its impact on mortality [93–96]. Additionally, cinacalcet increases risks of nausea, vomiting, and hypocalcemia, suggesting the harms may outweigh the benefits in this population [93].

In the IPPN registry, only 2.8% of 890 children were on cinacalcet and they were mainly from the USA [3]. There

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Table 63.4 Randomized controlled trials of active vitamin D treatment in children.

Author (year), country	Population, gender, age (years)	Study design, duration of treatment	Intervention (I), comparator (C)	*N* (I/C)	Primary outcome(s)	Result	Certainty of the evidence (GRADE)
Greenbaum (2005), USA [75]	CKD stage 5D, 66% male I: 15.3 ± 2.8 C: 14.0 ± 3.8	RCT, 12 weeks	Calcitriol IV thrice weekly (initial dose: 0.5 μg if PTH < 500 pg/ml, 1.0 μg if PTH 500 to 1000 pg/ml, 1.5 μg if PTH >1000 pg/ml) Placebo IV thrice weekly	47 (21, 26) 19 lost to follow-up	PTH decrease Change in biochemical parameters	• Calcitriol significantly increased the number of children who achieved a 30% decrease in PTH levels on at least two occasions (RR 2.72, 95% CI 1.12–6.61) • Changes in mean PTH levels during treatment were not significantly different between groups • Significantly greater risk of hypercalcemia (RD 0.24, 95% CI 0.05–0.43) and elevated serum calcium phosphorus products (RD 0.34, 95% CI 0.12–0.56) in children treated with calcitriol • No significant difference in the number with hyperphosphatemia between groups • Bone alkaline phosphatase was significantly reduced following intravenous calcitriol (mean difference 47.70 mg/l, 95% CI 88.54 to 6.86) • No significant difference in changes in levels of serum calcium, calcium phosphorus product, and phosphorus between groups	Moderate
Greenbaum (2007), USA [76]	CKD stage 5D, 76% male I: 13.6 ± 4.76 C: 14.3 ± 4.15	RCT, 12 weeks	Paricalcitol IV thrice weekly (initial dose: 0.04 μg/kg if PTH ≤500 and 0.08 μg/kg if PTH ≥ 500) Placebo IV thrice weekly	29 (15, 14) 17 did not complete study	PTH decrease Change in biochemical parameters	• Paricalcitol significantly increased the number of children who achieved a 30% decrease in PTH levels on at least two occasions during the study (RR 2.80, 95% CI 0.95–8.28) • No significant difference in changes in levels of serum calcium, calcium phosphorous product, and phosphorous between groups • No significant difference in the number with hypercalcemia between groups	Moderate

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Wesseling-Perry et al. (2011), USA [77]	CKD stage 5D, 50% male, 13.9 ± 0.5	2x2 factorial design, 8 months	Doxercalciferol orally thrice weekly Initial dose depended on PTH level, then titrated to keep PTH at 300 to 400 pg/ml and Ca 8.4 to 10.2 mg/dl Calcitriol orally thrice weekly	60 (30, 30), 9 did not complete study	Bone histomorphometry PTH decrease Change in biochemical parameters	• No significant difference in bone histology parameters of bone formation rate, percentage eroded bone, percentage osteoid volume, percentage osteoid surface, osteoid maturation time, and percentage bone volume between treatment groups • No significant difference in final PTH levels, but with significant decreases in PTH in both groups • No significant difference in final levels of calcium, phosphorus, serum alkaline phosphatase, and FGF 23 between treatment groups • Values of alkaline phosphatase fell significantly while values of FGF 23 rose significantly with both groups • No differences in episodes of hypercalcemia were seen between the two vitamin D therapies	Moderate
Schmitt et al., Europe [78]	CKD stages 3–5, 88% male I: 5.5 (2.4–8.4) years C: 5.1 (1.4–9.1) years (subset of participants included in Ardissino)	RCT, 12 months	Calcitriol orally twice weekly (35 ng/kg twice weekly, after 1 month, dose adjusted for PTH level) Calcitriol orally daily (10 ng/kg/day, after 1 month, dose adjusted for PTH level)	29 (14, 15), 5/29 lost to follow-up	PTH decrease Change in biochemical parameters Growth	• The average weekly dose of calcitriol did not differ between groups • Significant decrease in PTH levels in both groups, but no significant differences in the decrease in PTH levels at any time points between groups • No significant difference in mean integrated PTH at 12 months • No significant differences were found for change in calcium, phosphate, calcium-phosphate product, and alkaline phosphatase between groups • No significant difference in the change in mean height SDS	Moderate/ low
Ardissino et al., Europe [79]	CKD stages 3–5, 76% male, 8.4 ± 4.7 years	RCT, 8 weeks	Calcitriol orally twice weekly (35 ng/kg twice weekly) Calcitriol orally daily (10 ng/kg/day)	59 (30, 29), 85 enrolled, but only 59 included in 8-week analysis	PTH decrease Change in biochemical parameters	• The dose of calcitriol did not differ between groups (70.1 ± 3.4 ng/kg vs. 69.7 ± 4.3 ng/kg) • No significant differences in the decrease in PTH levels at 8 weeks between groups • No significant differences in the number with reduction in PTH at 8 weeks between groups	Moderate/ low

(*Continued*)

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Table 63.4 (Continued)

Author (year), country	Population, gender, age (years)	Study design, duration of treatment	Intervention (I), comparator (C)	*N* (I/C)	Primary outcome(s)	Result	Certainty of the evidence (GRADE)
						• No significant difference in the number of episodes of hypercalcemia or hyperphosphatemia between groups • No significant difference in the number of hypercalcemic or hyperphosphatemic patients between groups	
Watson (1988–1989), Canada [80]	CKD stage 5D, 67% male, I: 11.6 ± 6.0 C: 16.4 ± 14.0	Randomized trial, 6 months	1alpha-OH vitamin D orally 10–20 ng/kg/day Standard treatment	12 (6, 6)	Bone histology	• Children treated with 1alpha-OH vitamin D showed reduced osteoid volume	Moderate/low
					PTH decrease	• The number of children with PTH levels above the normal range of 3–25 pmol/l (RR 0.23, 95% CI 0.06–0.97) and the mean PTH levels (mean difference 55.00 pmol/l, 95% CI 83.03 to 26.97) were significantly lower in treated children compared with controls	
					Change in biochemical parameters	• No differences were reported in mean serum calcium and phosphorus levels at the end of treatment	
Webb (2017), multicenter, USA, Europe [81]	CKD 3–4, 10–16 years, 69% male I: 13.9 ± 1.8 years C: 13.3 ± 1.8 years	PK study, 48 h	3 μg paricalcitol	12 patients	Paricalcitol serum concentrations at 1, 2, 4, 6, 8, 12, 24, 36, and 48 h	• Adequate absorption of the drug with levels higher in children compared to adults with CKD, leading to the initial dosing of 1 μg three times weekly in all subjects (mean peak plasma concentration and area under the time curve from zero to infinity were 0.13 ng/ml and 2.87 ng × h/ml, respectively, for 12 children who received	
		RCT, 12 weeks and open-label extension phase, ≥12 weeks	Paricalcitol thrice weekly oral, placebo thrice weekly oral	36 (18,18), (16 and 13 completed this phase) 12 at each arm completed the study	PTH decrease	• 27.8% of the paricalcitol group achieved two consecutive iPTH reductions of ≥30% from baseline versus none of the placebo group ($P = 0.045$)	Moderate
					Adverse events	• Adverse events were higher in children who received placebo than in those administered paricalcitol during the double-blind treatment (88.9 vs. 38.9%, $P = 0.005$)	
	CKD 5, 39% male I: 14.5 ± 1.8 years	Paricalcitol, open label study, 12 weeks	Paricalcitol thrice weekly oral in all enrolled subjects	13 patients (11 completed the study)	PTH decrease	• 8 children (61.5%) had two consecutive iPTH reductions of ≥30% from baseline and 5 (38.5%) had two consecutive iPTH values of between 150 and 300 pg/ml	Moderate
					Hypercalcemia	• Clinically meaningful hypercalcemia occurred in 21% of children	

Ca, calcium; CKD, chronic kidney disease; FGF23, fibroblast growth factor 23; IV, intravenous; PTH, parathyroid hormone; RCT, randomized controlled trial; RR, risk ratio.
Sources: Adapted from Hahn et al. [56] and Webb et al. [81].

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Table 63.5 Summary of findings: active vitamin D therapy in children with CKD stage 2–5D.

Outcomes	No. of participants (no. of studies)	Absolute no. of patients affected per 1000 patients treated for 1 year (95% CI)	Relative risk (95% CI)	Certainty of the evidence (GRADE)	Conclusions
Bone disease	Three studies	Not estimable	Not estimable	Moderate/ low	Bone histology indicated improvement in children treated with vitamin D sterols No significant differences in bone histology were detected in studies comparing calcitriol and doxercalciferol
Growth	Two studies	Not estimable	Not estimable	Very low	No significant differences in growth rates were detected in studies comparing different vitamin D sterols
PTH control	Four studies	Not estimable	Not estimable	Moderate	No differences in PTH levels were found between oral daily and oral intermittent calcitriol therapy Vitamin D sterols given orally or intravenously resulted in reduced PTH levels compared with placebo or no specific treatment
Hypercalcemia	Five studies	Not estimable	Not estimable	Moderate	No differences in the number of children with hypercalcemia or the number of hypercalcemic episodes were found between oral daily or oral intermittent calcitriol therapy Hypercalcemic episodes were more common with intravenous calcitriol when compared with placebo Increased risk of hypercalcemia was not reported with 1alpha-hydroxyvitamin D or paricalcitol

Sources: Adapted from Hahn et al. [56] and Webb et al. [81].

are no pediatric RCTs on the use of cinacalcet in pediatric CKD before dialysis. Most of the data reporting the use of cinacalcet in pediatric CKD come from observational studies and small series [97–99]. Industry-sponsored trials have also been performed in pediatric dialysis patients (Tables 63.88 and 63.99) [100, 103, 104]. The first open-label study evaluated the safety, tolerability, pharmacokinetics, and pharmacodynamics of a single oral 15-mg dose of cinacalcet in pediatric subjects 6–17 years of age with CKD. No serious adverse events developed as a result of hypocalcemia [103]. The second study was conducted in infants and children under 6 years of age and a 0.25 mg/kg starting dose of cinacalcet was found to be safe, well-tolerated, and would result in a clinically meaningful decrease in PTH levels (−11% at 2 hours and −30% at 8 hours, returning to baseline at 72 hours) [104].

The third and only pediatric double-blind placebo-controlled phase 3 trial, including 43 patients between 6 and 18 years of age, randomized either cinacalcet or placebo and revealed that the effect of cinacalcet in reducing plasma iPTH was clinically meaningful and statistically significant despite early termination of the study following a fatality in a subject with severe hypocalcemia receiving cinacalcet. The cause of death was determined to be multifactorial, but a causal role for hypocalcemia could not be excluded [100]. Other industry-sponsored studies have only been presented as abstracts at international conferences [101, 102]. A phase 3 multicenter randomized open-label controlled study did not demonstrated efficacy of CIN, likely due to inadequate exposure [101]. On the other hand, an open-label, single-arm phase 2 study in dialysis patients aged 28 days to 6 years showed significant benefit of cinacalcet in reducing PTH levels with a good safety profile [102]. All three studies and their main characteristics are summarized in Table 63.8. After its approval by the European Medical Agency in 2017, a position statement on

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Table 63.6 Randomized controlled trials of native vitamin D treatment in children with CKD and dialysis.

Author (year), country	Population, gender, age (years)	Study design, duration of treatment	Intervention (I), comparator (C)	*N* (I/C)	Primary outcome(s)	Result	Certainty of the evidence (GRADE)
Shroff (2012), UK [87]	CKD with eGFR: 47 ± 8.1, 66% male, mean age I 10.6 ± 2.5 and C 7.9 ± 4.8	Randomized placebo-controlled trial, 52 weeks (median)	I: ergocalciferol (D2 orally) (dosing as per modified KDOQI 2005) (ref no: 1)	47 (24/23) enrolled, 20 in each arm completed study	The primary endpoint: time to development of hyperparathyroidism	Significantly longer with ergocalciferol vs. placebo (HR 0.30, 95% CI 0.09–0.93, $P = 0.05$) With ergocalciferol, normal 25(OH)D levels were achieved in all 8 children with CKD2, 8 of 11 children with CKD3, but not in the single patient with CKD4 There were no ergocalciferol-related adverse events	Moderate/ low

25(OH)D, 25-hydroxy vitamin D; CKD, chronic kidney disease; D2, vitamin D2; eGFR, estimated glomerular filtration rate; RCT, randomized controlled trial.
Source: Modified from Shroff [86].

Table 63.7 Suggested treatment for 25 hydroxy vitamin D supplementation in children with CKD and on dialysis.

Age	25(OH)D serum (nmol/l)	Vitamin D supplementation dose (daily)
Intensive replacement phase		
<1 year		600 IU/day[a]
>1 year		
	<12	8000 IU/day
	12–50	4000 IU/day
	50–75	2000 IU/day
Maintenance phase		
<1 year		
	>75	400 IU/day
>1 year		1000–2000 IU/day based on CKD stage

25(OH)D, 25-hydroxy vitamin D; CKD, chronic kidney disease.
[a] In infants <1 year, a fixed dose is recommended irrespective of the level of 25(OH)D.
Source: Modified from Shroff [86].

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Table 63.8 Randomized controlled trials of cinacalcet treatment in children.

Author (year), country	Population, gender, age (years)	Study design, duration of treatment	Intervention (I), comparator (C)	*N* (I/C)	Primary outcome(s)	Result	Certainty of the evidence (GRADE)
Warady (2017), multicenter [100]	CKD 5D, mean age 12.6 yr. (6 to <18 yr), 51% boys	Phase 3, randomized, double-blind, placebo-controlled study, 24-week dose titration period followed by a 6-week efficacy assessment phase (total 30 weeks)	I: cinacalcet Starting and maximum dose: 0.18 and 0.99 mg/kg/day C: placebo	22/21	Primary endpoint: ≥30% reduction from baseline in mean PTH during efficacy assessment phase	54.5% of subjects achieved the primary endpoint in the cinacalcet group, versus 19% in the placebo group ($P < 0.05$) with a difference of 35.5% (95% CI 8.76%, 62.24%) (CMH test $P = 0.017$) Study terminated early because of a fatality (multifactorial) Mean exposure time 110 vs. 123 days in control group The observed treatment effect of cinacalcet in reducing plasma iPTH was clinically meaningful and statistically significant despite early termination of the study	Not estimable
Schaefer (2017), multicenter [101]	CKD 5D, mean age 12.6 years (6–18 years), 51% male	Phase 3 multicenter randomized open-label controlled, 20 weeks	I: cinacalcet, starting dose 0.2 mg/kg Adjusted once-monthly up to 2.5 mg/kg/day (max. 180 mg) C: standard of care (SOC)	27/28 enrolled, (22/25 randomized)	iPTH reduction>30%	The proportion of subjects who achieved iPTH reduction>30% was not significantly different: 32% with cinacalcet + SOC, 22% with SOC (I = NS) Mean (SD) duration of exposure to CIN was 112.8 (41.0) days with average weight-adjusted daily dose of 0.398 (0.467) mg/kg/day Efficacy of CIN was not demonstrated likely due to inadequate exposure Frequent AEs in cinacalcet group: hypocalcemia (24.0%), muscle spasms (12.0%), nausea (12.0%), headache (4.0%) Four serious adverse events unrelated to cinacalcet	Moderate/low
Goodman (2017), multicenter [102]	CKD 5D, mean age 35.9 months (28 day to 6 years), 66.7% male	Phase 2, single-arm, open-label safety study, 26 weeks	All received cinacalcet + SOC Due to fatal event protocol changed: starting/max. daily dose of cinacalcet 0.25/4.20 mg/kg prior to hold ($n = 8$) and 0.20/2.50 mg/kg (max. 60 mg) after hold ($n = 10$)	17 children	Primary endpoint: the proportion of subjects who developed cCa < 9.0 mg/dl (28 days to <2 years) and <8.4 mg/dl (≥2 to <6 years) Secondary endpoints: percentage change of plasma PTH from baseline, ≥30% reduction from baseline in PTH, PTH < 300 pg/ml, and cCa < 8.8 mg/dl	No subject had a Ca value below the threshold for the primary endpoint Overall 70.6% of subjects showed >30% reductions in PTH from baseline 52.9% of subjects achieved PTH < 300 pg/ml during the study Mean cinacalcet exposure time: 86.7 days Mean daily starting dose and maximum dose were 0.18 (0.07) mg/kg and 0.73 (0.66) mg/kg, respectively	Moderate/low

AE, adverse event; Ca, calcium; cCa, corrected Ca; CIN, cinacalcet; CKD, chronic kidney disease; CMH test, Cochran–Mantel–Haenszel test; iPTH, intact parathyroid hormone; PTH, parathyroid hormone; SOC, standard of care.

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Table 63.9 Summary of findings: calcimimetic therapy.

Outcomes	No. of participants (no. of studies)	Absolute no. of patients affected per 1000 patients treated for 1 year (95% CI)	Relative risk (95% CI)	Certainty of the evidence (GRADE)	Conclusion
Reduction in PTH level	66 patients (three studies)	Not estimable	Not estimable	Very low	Cinacalcet may lead to a reduction in serum PTH levels
Hypocalcemia	66 patients (three studies)	Not estimable	Not estimable	Moderate	Hypocalcemia is a significant side effect and may be fatal in children having predisposing factors

PTH, parathyroid hormone.

the use of cinacalcet in pediatric dialysis patients based on the available data and opinion of experts from the European Society for Paediatric Nephrology and the ERA-EDTA was published [105]. There are no studies with etelcalcetide, the new IV calcimimetic, in children on dialysis.

Parathyroidectomy

Parathyroidectomy is recommended for hyperparathyroidism unresponsive to pharmacological therapy, including failure of calcitriol (with or without cinacalcet) to limit PTH rise, unacceptable side effects from treatment or adverse biochemical responses [106]. However, there is a complete lack of evidence on this topic even in adults and this procedure has its own complications and morbidity [106]. A recent meta-analysis showed that compared with standard treatment, parathyroidectomy significantly decreased all-cause mortality (RR 0.74 [95% CI 0.66 to 0.83], 15 cohort studies, 24 048 participants) and cardiovascular mortality (RR 0.59 [95% CI 0.46 to 0.76], six observational studies, almost 10 000 patients). Properly conducted, RCT comparing surgery with medical therapy and featuring many different outcomes from mortality to quality of life is necessary [107].

Growth Hormone

Growth retardation is a common complication of CKD [108] and one of the measures of quality of care in children. Recombinant human GH (rhGH) has been used successfully for many years to compensate growth failure in children and adolescents with CKD who are on conservative treatment, are undergoing dialysis or after kidney transplantation [19, 108–111]. In a recent Cochrane review, the efficacy, safety, and long-term results of rhGH were extensively evaluated. Treatment with rhGH (28 IU/m^2/week) compared with placebo or no specific therapy resulted in a significant benefit in children with CKD and on dialysis. One year of 28 IU/m^2/week rhGH in children with CKD resulted in a 3.88 cm increase in height velocity above that of untreated patients. Compared to the 14 IU/m^2/week group, there was a 1.18 cm/year increase in height velocity in the 28 IU/m^2/week group. Side effects of rhGH were generally similar to those of the control group [112]. A bone biopsy study in 33 PD patients showed that compared to placebo, GH therapy improved height irrespective of underlying bone histologic features. Additionally, normalization in bone formation rate was observed in those receiving rhGH therapy [113]. On the other hand, studies were too short to determine if continuing treatment resulted in an increase in final adult height [112] (Table 63.10).

Based on available data and recently published clinical practice recommendations, children with stage 3–5 CKD or on dialysis are candidates for GH therapy (0.045–0.05 mg/kg/day, subcutaneously) 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 [114]. Before rhGH treatment, all CKD-associated threats to growth, including protein-calorie malnutrition, metabolic acidosis, disturbances in fluid-electrolyte, and mineral metabolism, should be well controlled. Treatment is suggested to be maintained until the patient reaches the estimated target height or when epiphyseal growth plates fuse or until renal transplantation [114].

Conclusion

Systemic and bony manifestations of CKD-MBD are highly prevalent and lead to significant morbidity. Uniquely to children, in addition to remodeling abnormalities, modeling disturbances result in significant growth failure and skeletal deformities, which contribute to long-standing disability. The pathophysiology of CKD-MBD is incompletely understood and there are major gaps in the evidence for diagnosing the bone pathology and guiding treatment

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Table 63.10 Summary of findings: GH therapy in children with CKD stage 2–5D and kidney transplantation.

Outcomes	No. of participants (no. of studies)	Absolute no. of patients affected per 1000 patients treated for 1 year (95% CI)	Relative risk (95% CI)	Certainty of the evidence (GRADE)	Conclusion
	809 enrolled patients (16 RCTs)	Not estimable	Not estimable	Low	One year of 28 IU/m^2/week rhGH in children with CKD resulted in a 3.88 cm increase in height velocity above that of untreated patients Studies were too short to determine if continuing treatment resulted in an increase in final adult height The frequency of reported side effects of GH was generally similar to that in control groups
rhGH (28 IU/m^2/week) vs. placebo or no specific therapy					
Height SDS at 12 months	391 children (eight studies)	Not estimable	MD 0.82, 95% CI 0.56–1.07	Moderate	Delta height SD at 1 year: 0.82 (95% CI 0.56–1.07) in CKD patients, including dialysis and kidney transplantation patients
Height velocity at 6 months	27 children (two studies)	Not estimable	MD 2.85 cm/6 months, 95% CI 2.22–3.48	Low	The mean height velocity at 6 months of GH in the intervention groups was 2.85 cm higher than in controls
Height velocity after 1 year	287 children (seven studies)	Not estimable	MD 3.88 higher (95% CI 3.32 to 4.44)	Moderate	The mean height velocity after 1 year of GH in the intervention groups was 3.88 cm higher than in controls
Height velocity after 2 years	82 children (one study)	Not estimable	MD 2.30 cm/year, 95% CI 1.39–3.21)	Moderate/Low	The mean height velocity after 2 years of GH in the intervention group was significantly greater than in untreated children (2.3 cm/year)
rhGH 28 IU/m^2/week vs. 14 IU/m^2/week					
Height velocity after 1 year	150 children (three studies)	Not estimable	MD 1.18 cm/year with high dose, 95% CI 0.52–1.84	Moderate	1.18 cm/year higher height velocity after 1 year with high dose
rhGH daily subcutaneously [113]					
Height SDS	33 PD patients (one study)	Not estimable	Delta height SDS, GH vs. no-GH 0.32 ± 0.08 ($P < 0.01$)	Low	GH therapy improves height in pediatric dialysis patients, irrespective of underlying bone histologic features Therapy with growth hormone enhanced bone turnover in patients with baseline low bone turnover, while skeletal lesions of secondary hyperparathyroidism persisted in patients with high bone turnover at baseline, despite the concomitant use of calcitriol
Bone formation rate			Decreased in patients with high bone turnover from 103.3 to 60.3 μm^2/μm^3/year without rhGH ($P = 0.05$) Increased in patients with low bone turnover with rhGH (from 15.0 to 154.6 μm^2/μm^3/year ($P = 0.03$)		

CKD, chronic kidney disease; GH, growth hormone; MD, mean difference; rhGH, recombinant human growth hormone; SDS, standard deviation score.
Source: Adapted from Hodson [112].

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options. Measurement of PTH and biochemical bone remodeling markers is helpful but also lacks sensitivity and specificity, therefore therapeutic decisions should be based on to the trend in levels rather than single measurements. Also, there is a significant shift from treating to specific targets toward a more individualized approach to management. There is currently an absolute need for high-quality studies demonstrating the effectiveness of diagnostic and therapeutic interventions on patient-centered outcomes of children with CKD-MBD.

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Anemia

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Introduction

Anemia is one of the most common comorbidities in children with chronic kidney disease (CKD) and is associated with a variety of adverse consequences. A number of factors contribute to the development of anemia in children and adults with kidney disease, mainly dysregulated erythropoietin (EPO) production and iron restriction. As kidney function declines, patients experience a decrease in circulating red blood cell mass, indicated by low blood hemoglobin (Hb) concentration. The mainstays of anemia therapy in children with CKD are treatment with recombinant human erythropoietin (rHuEPO) and iron supplementation. A number of evidence-based clinical practice guidelines and recommendations for the monitoring and management of anemia of CKD in children, including the Hb thresholds used to define anemia, have emerged over the last 10–15 years and are summarized in this chapter.

Epidemiology

Data from the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) cohort has shown that the risk for anemia increases with advancing stage of CKD, with prevalence of 73% at stage 3, 87% at stage 4, and >95% at stage 5 [1, 2]. Within the Chronic Kidney Disease in Children (CKiD) cohort study, the median Hb declined as the measured glomerular filtration rate (GFR) decreased to <43 ml/min/1.73 m^2 [3]. In the International Pediatric Peritoneal Dialysis Network (IPPN) registry, low serum albumin, increased parathyroid hormone (PTH) levels, high serum ferritin, and the use of bio-incompatible dialysate were associated with low Hb [4, 5]. Race is also a recognized risk factor for anemia. Among children in CKiD, African American children demonstrated lower levels of Hb than white children, even after adjusting for level of kidney function [6]. Compared to adults on chronic dialysis in the United States, pediatric patients more often have mean annual Hb levels of <11 g/dl: (54% vs. 39.8% in pediatric compared to adult hemodialysis (HD) patients and 69.5% vs. 55.1% in pediatric compared to adult peritoneal dialysis patients [7]. Anemia remains a problem even after kidney transplantation. The prevalence of anemia post-transplant in one single-center study of 231 pediatric patients was 25.5% at 1 year after transplantation [8].

Pathophysiology

The kidneys play a central role in regulating red blood cell mass through the production of erythropoietin. Erythropoietin is synthesized by interstitial cells in the peritubular capillary bed of the renal cortex, but under conditions of injury these cells transdifferentiate in myofibroblasts that synthesize collagen and lose their erythropoietin-producing ability [9]. In addition to deficient erythropoietin production, it has been proposed that the kidney functions as a "critmeter" by sensing oxygen tension and extracellular volume, and translating a measure of plasma volume as tissue oxygen pressure to regulate erythropoietin production [10]. In CKD, diminished oxygen consumption by renal tissue leads to dysregulation of erythropoietin production independent of damage to erythropoietin-producing cells [10]. Nutritional problems during CKD and end-stage renal disease (ESRD) can lead

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to folate and vitamin B_{12} deficiency, leading to disordered DNA synthesis, maturation arrest, and ineffective erythropoiesis. Iron availability is a rate-limiting step in the maturation of red blood cells, and iron deficiency also further impairs erythropoiesis.

Inflammation, another common problem in CKD, impairs both erythropoiesis and the utilization of iron in red blood cell production. Inflammatory cytokines inhibit erythropoietin production and impair the growth of red blood cell progenitors [10]. A study by Goldstein et al. in 2006 found that the proinflammatory cytokines IL-1β, IL-6, IL-8, and tumor necrosis factor (TNF)-α are increased in pediatric patients compared to age-matched controls [11]. Inflammation also stimulates production of the iron regulatory-protein hepcidin, which is the key mediator of iron-restricted erythropoiesis in CKD. Hepcidin regulates both intestinal iron absorption and bodily iron distribution via suppression of cell membrane expression of ferroportin, the sole cellular iron exporter, by degrading ferroportin and inhibiting the release of iron stored in ferritin [12]. In 2009, Zaritsky et al. demonstrated that hepcidin levels are significantly increased in pediatric patients with CKD stages 2–5 compared to their respective controls, and that transferrin saturation and ferritin were predictive of hepcidin levels [13]. In a cross-sectional and longitudinal study examining hepcidin and its role in the development and progression of anemia in children with CKD, Atkinson et al. found that higher hepcidin levels were associated with a decreased Hb and increased risk of incident anemia [14].

Evidence has emerged to suggest an association between 25-hydroxy vitamin D (25-OHD) levels and anemia. Studies of the adult CKD population have shown that 25-OHD concentration is significantly correlated with Hb and decreased erythropoiesis-stimulating agent (ESA) dosing requirements [15]. in vitro treatment of mouse monocytes or hepatocytes with 25-OHD or 1,25-dihydroxy vitamin D by Bacchetta et al. was found to decrease hepcidin mRNA expression [16]. Additionally, in a pilot study of healthy human volunteers, a single oral dose of vitamin D_2 (100 000 international units [IU]) increased serum 25-OHD levels and decreased serum hepcidin levels by 34% within 24 hours of dose administration [16]. In a retrospective cohort study of pediatric CKD patients, 25-OHD insufficient/deficient patients were twice as likely to be anemic and that there was a significant correlation between 25-OHD level and Hb [17]. However, a recent pilot randomized controlled trial showed that treatment of pediatric CKD patients with 4000 IU of cholecalciferol daily compared to 400 IU daily was not associated with a significant change in hepcidin level at 4 or 12 weeks, despite median C-reactive protein level decreasing significantly in the 4000 IU daily group [18]. Further randomized clinical trial (RCT)s may be useful to describe the relationship between vitamin D, hepcidin and anemia, and to continue to explore the effect of hepcidin modification on the treatment of anemia.

Diagnosis

Suggested Hb thresholds for the diagnosis of anemia in children with CKD are presented in Table 64.1. There have been a series of clinical practice guidelines for the diagnosis and management of the anemia of CKD published over the last 10–15 years, which are summarized in this section. In 2006 in the United States, the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) published clinical practice guidelines for anemia in CKD based on an evidence-based review. The KDOQI pediatric workgroup defined anemia in a child as a reduction in Hb level to less than the fifth percentile for their age and sex, with the caveat that adjustment in normal levels should be done for children living at higher altitudes. The

Table 64.1 Definitions of anemia in children with CKD.

KDOQI		
	5th percentile Hb level (g/dl)	
Age group (years)	**Boys**	**Girls**
1–2	10.7	10.8
3–5	11.2	11.1
6–8	11.5	11.5
9–11	12.0	11.9
12–14	12.4	11.7
15–19	13.5	11.5

KDIGO	
Age group (years)	Hb level (g/dl)
0.5–5	<11.0
5–12	<11.0
12–15	<12.0
>15 and adult	<13.0 (males) <12.0 (females)
RA	
Age group (years)	Hb level (g/dl)
<2	Hb 10.5
≥2	Hb 11

Source: Adapted from the KDOQI [19], KDIGO Anemia Workgroup [20], and Mikhail et al. [21].

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normative values for children older than 1 year of age published in the KDOQI guidelines were adapted from data from the National Health and Nutrition Evaluation Survey III reference data [22] (Table 64.1), whereas the values for children from birth to 1 year of age were derived from the textbook *Hematology of Infancy and Childhood* [23].

In 2012, the international Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Workgroup published guidelines on diagnosis and management of anemia for both adult and pediatric patients with CKD. The diagnosis of anemia in pediatric CKD patients was recommended for Hb concentration <11 g/dl for children 6 months to 5 years old, <11.5 g/dl for 5–12 years old, and <12 g/dl for 12–15 years old [20]. The most recent clinical practice guidelines regarding anemia in CKD were published in 2017 by the Renal Association (RA) in the United Kingdom. The diagnosis of anemia in pediatric patients was recommended at a Hb level of 10.5 g/dl in children younger than 2 years old and at a Hb level of 11 g/dl in children >2 years old [21].

In the development of the KDOQI guidelines, a systematic literature review was performed of Hb thresholds for initiating therapy, Hb level therapeutic goals, iron status goals, and efficacy of adjuvants in achieving Hb goals. For the pediatric population, clinical practice recommendations were made in the absence of pediatric-specific evidence. As stated by the committee, "the only evidence of sufficient strength to support evidence based guidelines are available from studies of the adult population" [19]. The workgroup included clinical practice recommendations on evaluation of anemia in CKD (Table 64.2), target Hb range (>11 g/dl), use of ESAs and iron agents, as well as adjuvants, transfusion indications, and evaluation of persistent failure to reach or maintain intended Hb level.

Table 64.2 Recommendations for anemia evaluation in pediatric CKD.

CBC, including MCH, MCV, MCHC, and WBC with differential and platelet counts
Absolute reticulocyte count
Serum ferritin
Transferrin saturation
Serum vitamin B12 and folate levels[a]
Tests for hemolysis (haptoglobin, lactate dehydrogenase, bilirubin, Coombs' test)[b]

CBC, complete blood count; MCH, mean corpuscular Hb; MCV, mean corpuscular volume; MCHC, mean corpuscular Hb concentration, WBC, white blood cells.
[a] Recommended for all patients in KDIGO guidelines.
[b] Only recommended in selected cases per RA guidelines.
Source: Adapted from the KDOQ& National Kidney Foundation [24], KDIGO Anemia Workgroup [20], and Mikhail et al. [21] recommendations.

In 2007 KDOQI, in response to data from adult trials in which use of ESA to target higher Hb levels was associated with adverse outcomes, published a revised recommendation advising that in patients receiving ESA the Hb target should generally be in the range of 11–12 g/dl and should not exceed 13 g/dl [19].The Caring for Australians with Renal Impairment (CARI) group [25] systematically reviewed the evidence and determined that no evidence-based recommendations were possible based on level 1 or 2 evidence in 2005. In suggestions for clinical care, they stated that there was no evidence to support that treatment of anemia improves growth in pediatric CKD cases; however, correction of anemia is indicated to improve quality of life (QoL) and cardiac performance. In 2003, the European Pediatric Peritoneal Dialysis Working Group published guidelines on the management of anemia in pediatric peritoneal dialysis patients. These guidelines stated that after a thorough diagnostic workup, anemia treatment should aim for a target Hb concentration of at least 11 g/dl through administration of erythropoietin and iron preparations. According to these guidelines, iron should preferably be prescribed as an oral preparation, and there is no place for carnitine supplementation in the treatment of anemia in pediatric peritoneal dialysis patients [26].

The National Institute for Health and Care Excellence (NICE) in the United Kingdom periodically updates its guidelines, most recently in 2015. The NICE group recommended that oral iron be trialed prior to intravenous (IV) iron in patients who are not on hemodialysis, and that iron deficiency be addressed prior to initiation of ESAs. For patients who are on ESAs, the recommended Hb target was 10–12 g/dl in children >2 years old and adults, and 9.5–11.5 g/dl in children younger than 2 years old [27].

The KDIGO guidelines were created from systematic literature searches and supplemental evidence from October 2010 to March 2012. The workgroup provided clinical practice recommendations for the diagnosis and evaluation of anemia in CKD, use of iron, use of ESAs, and use of red cell transfusions for treatment of anemia in CKD. For pediatric patients, oral iron (or IV iron in hemodialysis-dependent patients) was recommended for transferrin saturation ≤20% and ferritin ≤100 ng/ml. They did not recommend a Hb threshold for initiation of ESAs in pediatric patients, but recommended that providers consider all potential benefits and harms prior to starting ESA therapy. For pediatric patients on ESAs, the target Hb recommended was 11–12 g/dl [20]. Finally, the RA guidelines utilized systemic literature searches and a review of related guidelines including NICE, KDOQI, and KDIGO. Oral iron was recommended for all anemic patients not on hemodialysis, with reservation of IV iron for patients with severe iron deficiency or who are on hemodialysis. For patients on IV

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iron therapy, a high-dose/low-frequency regimen was recommended. ESAs were recommended for patients who would benefit from them in terms of QoL, functioning, and to avoid blood transfusions. The target Hb for patients on ESAs was 10–12 g/dl for children >2 years and adults, and 9.5–11.5 g/dl for children <2 years [21]. The most recent specific recommendations for anemia treatment from KDIGO and the RA are presented in Table 64.3, including

Table 64.3 Anemia monitoring and treatment clinical practice recommendations from KDIGO and RA.

	KDIGO		RA	
Parameter	**Iron**	**ESAs**	**Iron**	**ESAs**
Frequency of monitoring	Hb monitored every 3 months in CKD stages 3–5 (nondialysis) and in PD patients; monthly in HD patients	Hb monitored monthly during initiation phase and every 3 months during maintenance phase for nondialysis patients, monthly for dialysis patients; TSAT and ferritin monitored every 3 months during ESA therapy or more frequently when initiating or increasing ESA dose, in case of blood loss, after course of IV iron	Hb monitored annually in CKD stage 3, twice/year in CKD stages 4–5; iron stores monitored every 1–3 months in patients on IV iron; ferritin >800 μg/l with normal CRP may suggest iron overload	Hb monitored every 2–4 weeks in correction phase and every 1–3 months for maintenance phase
Goals	TSAT >20%; ferritin >100 ng/ml; address correctable causes of anemia (including iron deficiency and inflammation) prior to starting ESA	Hb goals: 11–12 g/dl in all pediatric patients	%HRC < 6%, CHr > 29 pg/ferritin, TSAT > 20%, ferritin > 100 ng/ml; correct iron-deficiency prior to starting ESA	Hb goals: <2 years old 9.5–11.5 g/dl ≥2 years old 10–12 g/dl
Dosing	For pediatric patients, PO iron recommended in non-HD patients, IV iron recommended for HD patients	Determined by initial Hb concentration, body weight, and clinical scenario	High dose, low frequency recommended for IV iron	Determined by initial Hb level, target Hb level, and rate of increase in Hb
Contraindications	Active systemic infections	Provider to balance benefit of reducing blood transfusions with risk of stroke, loss of vascular access, hypertension; use caution with active or history of malignancy, history of stroke		Severe hypertension; use caution prescribing ESAs for history of stroke or malignancy
Route of administration	Determined by severity of iron deficiency, availability of venous access, response to prior PO iron, side effects, patient compliance, cost. For nondialysis patients, PO iron preferred; use IV iron for HD patients	Determined by treatment setting; SC ESA recommended for nondialysis and peritoneal dialysis patients; IV ESA recommended for HD patients	Determined by clinical condition and treatment setting; PO iron preferred in non-HD patients; IV iron reserved for severe iron deficiency and HD patients	Determined by clinical condition and treatment setting; SC ESA preferred in non-HD patients; IV ESA preferred in HD patients
Frequency		Determined by CKD stage, treatment setting, efficacy, patient tolerance, and preference, type of ESA	Low frequency recommended for IV iron	Determined by CKD stage, treatment setting, class of ESA; less frequent administrations with long-acting ESAs preferred in non-HD patients

IV, intravenous; HD, hemodialysis; PD, peritoneal dialysis; PO, by mouth; SC, subcutaneous; TSAT, transferrin saturation.
Source: Adapted from the KDIGO Anemia Workgroup [20] and Mikhail et al. [21] recommendations.

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recommended frequency of Hb iron store monitoring and routes of therapy.

Prognosis

Risk of Death

Studies in adults with ESRD have consistently demonstrated reduced risk of death and hospitalization when Hb levels are ≥11 g/dl, but the upper limit of target Hb is more controversial [28–30]. In 2004, the Cochrane Renal Group performed a meta-analysis of RCTs to evaluate the harms and benefits of different Hb targets in adult patients with CKD; they found lower risk of all-cause mortality with Hb of <12 versus >13 g/dl (relative risk [RR] 0.84, 95% confidence interval [CI] 0.71–1.00) [31]. This Cochrane review was updated in August 2006, included 22 RCTs, and had similar results [32]. The authors indicated the need for more adequately powered and better-designed trials. In November 2006, two additional RCTs investigating optimal target Hb were published [33, 34]. Drueke et al. randomly assigned 603 patients with estimated GFRs of 15–35 mL/min/1.73 m^2 and Hb of 11–12.5 g/dl to a target Hb of 13–15 g/dl versus Hb of 10.5–11.5 g/dl. Over 3 years, they found that early complete correction of anemia did not reduce risk of cardiovascular events in patients with CKD.

In children, there is less systematic evidence concerning the risks of anemia in CKD, and clinical practice guidelines and recommendations for anemia management are often primarily based on adult studies. However, lower Hb levels in children on dialysis have been strongly and independently associated with increased risk for mortality in observational studies of children on dialysis. In the pediatric population, Warady and Ho demonstrated an association between baseline hematocrit of <33% at 30 days postinitiation of dialysis and increased risk of prolonged hospitalization and death in incident ESRD patients less than 18 years of age from the NAPRTCS registry [35]. Using data from the US Centers for Medicare and Medicaid Services' ESRD Clinical Performance Measures Project (October–December 1999 and 2000) linked with the US Renal Data System hospitalization and mortality records, Amaral et al. assessed whether achieving target Hb levels of >11 g/dl in 677 adolescents on HD was associated with decreased risk of death. In this retrospective cohort study, 11.7% with Hb of <11 g/dl at study entry died compared to 5% of those with initial Hb of ≥11 g/dl ($P < 0.0001$) [36]. In the multivariable analysis, Hb of ≥11 g/dl was associated with decreased risk of death (hazard ratio [HR] 0.38, 95% CI 0.20–0.72). When Hb was recategorized into Hb levels of <10, ≥10 to <11, ≥11 to ≤12, and >12 g/dl, risk of mortality declined as Hb level increased. At Hb levels of 11 to ≤12 g/dl versus <10 g/dl, mortality risk decreased by 70% (HR 0.30, 95% CI 0.19–0.74). Risk of mortality was similar for Hb levels of 11–12 g/dl and >12 g/dl. Hb of >12 g/dl remained strongly associated with decreased risk of mortality (HR 0.20, 95% CI 0.07–0.56) [36]. This observational study's findings were consistent with literature on adults, showing decreased mortality in ESRD patients who meet Hb targets of >11 g/dl for adolescents on HD.

In 2013 Borzych-Duzalka et al. found that anemia, defined as Hb <10 g/dl in children aged 2 and over and <9.5 g/dl in those younger than 24 months according to the NICE guideline, was associated with increased risk for mortality and that the risk for death on dialysis was independently inversely associated with Hb [5]. Examining the US pediatric peritoneal dialysis population, Dahlinghaus et al. found that Hb ≥11 g/dl was associated with lower hospitalization risk but not with decrease in mortality risk. Hb levels ≥12 g/dl were not associated with decreased risk of hospitalization compared to levels of 11–12 g/dl [37]. Published in 2017, a 40-year retrospective cohort study of children on renal replacement therapy (RRT) by Adamczuk et al. found that mean Hb level was higher among survivors compared to nonsurvivors and was a significant prognostic indicator. The survivors were more frequently treated with ESAs, suggesting that treatment of anemia is important in decreasing mortality in patients on RRT [38].

There are currently no pediatric clinical trial data to support a Hb target above the current target of 11 g/dl. Future studies in the form of RCTs are needed to assess optimal Hb levels for all adolescents with CKD and ESRD. The KDIGO Anemia Workgroup stated that pediatric Hb targets are based on adult studies due to limited pediatric evidence, but recognized that a Hb less than 9.9 g/dl has been associated with increased risk of mortality and left ventricular hypertrophy (LVH), and recommended a Hb target of 11–12 g/dl for pediatric patients [20]. The RA recommendations are slightly different, with the lower limit of acceptable Hb being 9.5 g/dl for children younger than 2 years old and 10 g/dl for children 2 years or older. The recommended upper limit of Hb also varies by age, with 11.5 g/dl recommended for children less than 2 years old and 12 g/dl for children 2 years or older [21]. However, recently in a retrospective cohort study, Rheault et al. found that a Hb above 12 g/dl was not associated with increased risk of arrhythmia, cardiac arrest, or cerebrovascular accident (compared to Hb of <10 or 10–12 g/dl). Compared to the groups with lower Hb levels, the group of patients with Hb >12 g/dl had a lower hazard ratio of all-cause mortality and rate of all-cause hospitalizations [39]. Given this information, an upper limit of 12 g/dl is reasonable, but further information from RCTs would be useful to find the optimal Hb target for pediatric CKD patients.

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Risk of CKD Progression

A number of studies have suggested that anemia may accelerate decline in kidney function through decreased oxygen delivery to tissues, accelerating ischemic changes and increasing endothelial injury. It has been proposed that hypoxia of renal tubule cells may stimulate extracellular matrix production and release of profibrotic cytokines, thereby accelerating kidney disease progression. Several clinical trials in adults have suggested that EPO treatment and correction of anemia may ameliorate the progression of CKD [40]. In 2007 a prospective cohort study by Furth et al. demonstrated an association between anemia and accelerated progression of CKD in 23 adolescents enrolled in the CKiD study, independent of GFR [41]. However, a subsequent analysis performed in 398 CKiD subjects found that in multivariable analysis, glomerular disease, proteinuria, hypertension but not anemia were associated with accelerated GFR decline [42]. More evidence is needed to support the theory that treatment of anemia slows progression of CKD.

Anemia, Quality of Life, and Cognitive Function

Anemia of CKD has long been associated with a negative impact on QoL. Several studies have revealed that the treatment of anemia in CKD improves QoL in adults with CKD and ESRD [43–46]. One single, blinded, placebo-controlled crossover study in 11 children with ESRD showed improvement in exercise tolerance, physical performance and health, and better school attendance with correction of anemia [47]. Decreasing anemia using rHuEPO in a multicenter pediatric study of 44 children with chronic kidney failure undergoing HD also showed marked improvement in QoL, particularly in activity levels [48]. Another cross-sectional study, by Gerson et al., examined the link between QoL and anemia in a cross-section of 116 adolescents with renal insufficiency on dialysis and post kidney transplantation. The authors found that anemia was associated with poorer QoL [49]. By caregiver assessment, adolescents with kidney disease and anemia (defined as hematocrit of <36%) were less satisfied with their health, participated in fewer activities at school and with friends, and were less physically active. These findings mirrored findings of studies examining the correlation between anemia and QoL in adults with CKD.

Regarding cognitive function, one multicenter trial of subcutaneous erythropoietin showed increased Wechsler intelligence scores in 11 children with chronic kidney failure who were treated for anemia over a 12-month period [50]. In the adult literature, several studies have demonstrated significant improvement in electrophysiological markers of cognitive function with improvement of anemia in patients with chronic and ESRD [34, 51–55]. Further study in the pediatric population is needed.

Cardiac Function

In adults, observational evidence has shown an association between anemia and LVH [56, 57]. Optimal Hb levels to prevent LVH and cardiovascular events are not clear based on the current body of evidence [58, 59]; some studies have suggested increased risk at higher Hb levels. Volkova and Arab performed an evidence-based literature review of the relationship between Hb and/or hematocrit and mortality in dialysis patients. They included five trials and 13 observational studies. They showed either no effect or a benefit of Hb level target higher than 11 g/dl in a general dialysis population and increased mortality associated with greater Hb concentration in cardiac patients [60]. They concluded that "most observational studies supported the increased mortality associated with Hb levels less than the reference range of Hb 11–12 g/dl (110–120 g/l)," and that "evidence of risks or benefits of Hb levels greater than 11–12 g/dl (110–120 g/l) is variable" [60].

Evidence supporting cardiac benefits associated with the treatment of anemia in children with CKD is more limited, although cardiac-related events and LV remodeling have been reported in pediatric CKD and ESRD populations, including children after kidney transplantation [61–63]. According to the KDOQI reviews, a single blinded crossover trial of 11 children aged 2–12 years on dialysis demonstrated an improvement in cardiac index by 6 months and significant reduction in LV mass by 12 months in those treated with ESAs [64]. Two additional observational studies of patients with severe LVH demonstrated that children with lower Hb levels had more severe LVH and lower LV compliance [65, 66]. A 2-year longitudinal study of children with CKD showed that initial lower Hb level was associated with increased incident LVH and independently predicted an interval increase in LV mass index [67]. In 478 children in the CKiD cohort, anemia was found to be an independent predictor of LVH even when controlling for systolic and diastolic blood pressure [68].

Treatment

With the isolation of the human *EPO* gene in 1985 and the commercial production of rHuEPO soon after, ESA became a critical component of the treatment of the

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anemia of CKD in patients of every age. The United States Food and Drug Administration approved epogen for the treatment of the anemia of CKD in 1989, and its widespread use virtually eliminated the dependence on red blood cell transfusions that previously plagued patients with kidney disease [69]. There are several types of short- and long-acting ESAs available worldwide. Among rHuEPO types, epoetin alfa is commonly used in the US and epoetin beta used in Europe. Darbepoetin alfa is an EPO analogue with two additional sialic-acid-containing carbohydrates resulting in extended *in vivo* biological activity [70, 71]. Epoetins are short-acting and are generally dosed one to three times per week. Darbopoetin is long-acting and can be dosed weekly or every 2 weeks. A more recently developed EPO analogue is the continuous EPO receptor activator (CERA), which integrates a large methoxy polyethylene glycol polymer chain into the EPO molecule, resulting in higher molecular weight and longer half-life, allowing for extended monthly doses [69].

Table 64.4 summarizes pediatric studies examining the safety and efficacy of ESAs in anemia of CKD and ESRD. In children who require ESA treatment, there are several types of both long- and short-acting ESAs, and new formulations continue to emerge; this requires ongoing attention to the relative safety and efficacy in children overall and compared to adults. In a study published in 2006 Warady et al. randomized 124 children on stable rHuEPO to either continue on rHuEPO or convert to darbepoetin. The authors detected no statistically significant difference in mean change in Hb between the two groups, and since that time darbepoetin has been frequently utilized for the treatment of anemia in children [72]. In 2018, Warady et al. reported that Hb response was equivalent when darbepoetin was dosed either weekly or every other week, confirming the efficacy of a less frequent and potentially more patient-friendly treatment regimen [74]. CERA agents are also emerging for the treatment of anemia of CKD in children. In a study of 16 children on peritoneal dialysis (PD) previously treated with twice-weekly rHuEPO, CERA effectively and safely maintained Hb > 11 g/dl when dosed once or twice per month [73]. Subsequently in a cohort of 64 children on HD aged 5–17 years of age, maintained on stable doses of epoetin alfa/beta or darbepoetin and converted to a CERA dosed once every 4 weeks, Hb levels were effectively maintained within the target range of 10–12 g/dl after conversion with no additions to known safety profile [75].

A summary of the clinical practice recommendations published by the KDIGO [20] UK-based RA [21] and pediatric workgroup of the KDOQI [24] groups is included in Table 64.5. There is little available evidence in the form of RCTs to assess differential efficacy between ESAs in children or adults with CKD (Tables 64.4 and 64.5). Thus, because there are some data in pediatrics supporting the adult findings and no data supporting differing recommendations, the current practice recommendations have often been adapted from the evidence-based recommendations in adults. Although there are several potential benefits associated with ESA use, clinical trials in adults have raised concern about the safety of using escalating ESA doses to normalize Hb. The Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) trial performed in adults with nondialysis CKD found that using epoetin alfa to target higher Hb was associated with increased risk for death, myocardial infarctionI, stroke, or congestive heart failure [34]. In the 2009 TREAT trial, adults with CKD receiving darbepoetin to achieve Hb > 13 g/dl demonstrated increased risk for stroke [77]. Consequently, in 2001 the US FDA changed the ESA product labeling to recommend the lowest possible ESA dose to prevent red blood cell transfusions, and that the dose should be reduced or interrupted for Hb > 11 g/dl [78]. However, this label change did not distinguish between pediatric and adult CKD patients. Although no such randomized controlled trials have been conducted in pediatric patients, observational data has demonstrated that higher ESA doses are associated with increased risk for mortality in children on chronic dialysis [5, 37, 76] (Table 64.6). No clinical trials in adults have identified whether the higher Hb level or the higher ESA dose specifically contributes to increased risk for adverse outcomes, but a prospective study in adults on dialysis found that those with naturally occurring higher Hb levels >12 g/dl were not at increased risk for mortality [79, 80]. In a similar study conducted in children on dialysis, Rheault et al. demonstrated that Hb level >12 g/dl was not associated with increased risk for either mortality or hospitalization [39].

Hb Monitoring

In general, it is recommended that Hb be monitored monthly, with closer monitoring at 1–2-week intervals when initiating and/or making significant changes to the ESA dose. All pediatric providers are advised to carefully

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Table 64.4 Pediatric studies examining safety and efficacy of erythropoiesis stimulating agents (ESAs) in anemia of CKD and ESRD for pediatric patients.

Reference[a]	Type	Population	Intervention	Sample Size	Follow-up	Outcome
Sinai-Trieman et al. [102]	Prospective cohort	Transfusion-dependent PD pts	SC rHuEpo: initial dose 150 units/kg thrice weekly	5 children, 12–18 years old	8 months	All patients had increase in Hb and reticulocyte count and none required further transfusions
Offner et al. [103]	Prospective cohort	CAPD and CCPD	300 units/kg IV rHuEpo once weekly	14 children, 6–22 years old	1 year	Mean HCT and retic. count increased within 1 month Dosage was decreased after 3 months to keep HCT > 30%.
Campos and Garin [104]	Prospective cohort	HD	IV rHuEpo: thrice weekly	11 children, 6 months to 20 years old	9 months	HCT rose after 8 weeks from 20.3% (mean) to 31.7%
Reddingius et al. [105]	Prospective cohort	CAPD	IP rHuEpo: initial dose 300 units/kg/week	16 children	8 months	Mean Hb increased No patients required blood transfusions after initiation of therapy
Montini et al. [106]	Prospective cohort	PD	SC rHuEPO: initial dose 25 IU/kg twice weekly	24 children	24 weeks	6 patients censored, 18 remaining patients all had increased Hb
Brandt et al. [107]	Prospective randomized study	CKD, PD, and HD patients	IV or SC rHuEPO: low-dose (150 units/kg/week) vs. high-dose (450 units/kg/week) divided thrice weekly	44 children <21 years old: 25 pre-dialysis, 10 PD, 9 HD	12 weeks or until "target" Hb was attained	82% patients reached "target" Hb by 8 weeks; 95% patients in high-dose group reached target vs. 66% in low-dose group HD patients required higher doses
De Palo et al. [108]	Prospective cohort	HD patients previously on epoietin alfa	Darbepoetin 1.59 ± 1.19 μg/kg/week	7 children	6 months	Increase of >1 g/dl Hb in first month By second month, dose reduced Mean Hb at 3 months 11.8 ± 1.4 g/dl and mean darbepoietin dose 0.51 ± 0.51 μg/kg/week
Geary et al. [109]	Prospective cohort	CKD with GFR <30 ml/min/1.73 m^2, HD and PD patients	Darbepoetin alfa 0.45 μg/kg/week	23 children	28 weeks	73% of patients were receiving darbepoetin less than once weekly by 12 weeks and 87% by 28 weeks to maintain Hb 10–12.5 g/day
Durkan et al. [110]	Prospective cohort	Infants with CKD <8 kg	Darbepoetin 0.5 μg/kg/week	6 infants	20 weeks	For 3 patients mean darbepoietin dose was decreased and dosing interval increased to 3–4 weeks 3 patients required increase in weekly dose

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Warady et al. [72]	Randomized open-label, noninferiority study	CKD with GFR <30 ml/min/1.73m^2, HD and PD patients who were receiving stable rHuEpo treatment	Subjects randomized (1 : 2) to either continue rHuEpo or convert to darbepoetin alfa	124 children, aged 1–18 years, receiving stable rHuEpo	28 weeks	Adjusted mean change in Hb between baseline and evaluation period for rHuEpo vs. darbepoetin groups was not statistically different Darbopoetin was found to be noninferior to rHuEpo
Cano et al. [73]	Prospective cohort	PD patients previously stable (Hb > 10 g/dl) on epoetin alfa with ferritin > 100 μg/l and TSAT > 20%	Methoxy polyethylene glycol epoetin beta (Mircera®) administered SC, starting dose 0.5 μg/kg q 2 week, dose adjusted to achieve Hb ≥ 11 g/dl	16 patiens aged 2–14 years	6 months	Mircera effectively maintained Hb levels when administered once or twice monthly Doses required to reach target Hb were higher than published experiences in adults
Schaefer et al. [111]	Prospective cohort	Children ≤16 years on PD, HD, or with CKD (eGFR < 60 ml/min/1.73 m^2) and receiving darbepoetin alfa Withdrawal for transplant or cessation of darbepoetin alfa	Darbepoetin alfa treatment regimen altered by treating physicians	319 patients who received at least one dose of darbepoetin alfa	Up to 2 years	No new safety signals associated with darbepoetin alfa use were reported Weight-adjusted dose to maintain Hb was consistently higher in younger than older children
Warady et al. [74]	Double-blind, randomized controlled trial	ESA-naïve, anemic children with CKD aged 1–18 years, including stage 3–5 CKD, HD, and PD TSAT ≥ 20% and Hb < 10 g/dl at initiation	Initial dose of darbepoetin alfa of 0.45 μg/kg week vs. 0.75 μg/kg every other week Administered SC in CKD and PD, IV in HD Subsequent doses were titrated to achieve target Hb 10–12 g/dl	114 patients	25 weeks	Correction of Hb to ≥ 10 g/dl occurred in >80% of subjects in either the weekly or q 2-week dosing groups
Fischbach et al. [75]	Phase II open-label trial, multiple-dose study	HD 5–17 years with Hb 10–12 g/dl on epoetin or darbepoetin	IV CERA dosed every 4 weeks at two starting doses and titrated: −4 μg for each weekly dose of 250 IU epoetin alfa/beta or 1.1 μg darbepoetin OR −4 μg for each weekly dose of 125 IU epoetin alfa/beta or 0.55 μg darbepoetin	64 patients	20 weeks	Using CERA conversion factor of 4 μg for each weekly dose of 125 IU epoetin alfa/beta or 0.55 μg darbepoetin, 81% of patients maintained Hb in 10–12 g/dl range and 75% maintained Hb within 1.0 g/dl of baseline

HCT, hematocrit; IP, intraperitoneal; IV, intravenous; rHuEpo, recombinant human erythropoietin; SC, subcutaneous.
[a] References listed in reference section.

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Table 64.5 Erythropoiesis stimulating agents

Intervention	Systematic review	Evidence rating[a]	Comment on rating	Recommendations[b]	Comment on recommendation
Initiation of ESA	No RCTs examining effects of ESA on hard outcomes (KDIGO)	Very low (KDIGO) Moderate (RA)	Upper and lower Hb targets are opinion based (KDIGO)	Hb concentration at which ESA is initiated should weigh potential benefits and harms (KDIGO) Should be offered to patients likely to benefit and to avoid RBC transfusion (RA)	No specific Hb threshold for ESA initiation identified, but limited data that children with Hb < 9.9 g/dl are at increased risk for adverse outcomes
Choice of ESA	No evidence that any given ESA brand is superior to another with regard to patient outcomes (KDIGO)	Very low (KDIGO) Moderate (RA)	In studies in adults and children, all available products are efficacious when administered according to manufacturer's recommendations (RA)	Choose ESA based on balance of safety, cost, and availability, using only agents approved by independent regulatory agency (KDIGO) Decision should be based on local availability (RA)	
Target Hb concentration on ESA	Observational data only that lower Hb associated with morbidity (KDIGO)	Very low (KDIGO) Moderate (RA)	Caution in targeting higher Hb based on data extrapolated from adult trials only (KDIGO)	Keep Hb in range of 11–12 g/dl (KDIGO) Keep Hb 10–12 g/dl in children 2 and older, 9.5–11.5 in <2 year-olds (RA)	Lower Hb target in <2 year-olds based on lower normal range in age group
ESA dose – initiation	No primarily pediatric studies	Very low (KDIGO) Moderate (RA)	Initial dosing information determined from adult studies	Determine initial ESA dose based on Hb, weight, and clinical circumstances (KDIGO) Initial dose baseline on Hb, Hb goal (RA)	EPO starting dose 20–50 IU/kg 3 times/week, DA 0.45 μg/kg/week. – IV or SC (KDIGO) Goal of initial therapy to raise Hb by 1–2 g/dl/month, route determined by patient and ESA factors (RA)
ESA dose – maintenance	No primarily pediatric studies	1) Moderate 2) Low (KDIGO) 3) Moderate 4) Ungraded (RA)	Extrapolated from adult studies	5) Adjust ESA dose based on Hb and rate of change 6) Decrease ESA dose done rather than withhold (KDIGO) 7) Adjust ESA dose for Hb < 10.5 or >11.5 in patiens ≥2 years 8) For <2 year-olds, adjust before level is outside range to avoid fluctuation (RA)	EPO dose can be increased q 4 weeks by weekly dose of 3 × 20 IU/kg If Hb is increasing and approaching 11.5 g/dl, dose should be reduced by ~25% (KDIGO) Children may require higher absolute ESA doses compared to adults

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			KDOQI 2006		
rHuEpo once weekly vs. twice weekly in dialysis patients	Cochrane Review, 2005 : 11 RCT of 719 patients	Moderate	The duration and frequency of the studies differed and there were small numbers of participants	There is insufficient evidence to recommend one regimen of frequency of rHuEpo dosing	There was no significant difference between once weekly vs. twice weekly dosing Large RCTs with longer duration and greater numbers of subjects are needed
ESA vs. placebo in HD and PD patients	12 RCT, including one pediatric[c]	Moderate	The duration, dosing frequency, and outcomes of the studies differed	The current body of evidence is insufficient to recommend one ESA agent or dosing pattern and potential benefits and risk must be weighed for each patient	ESAs are effective for reducing the requirement for blood transfusions in ESRD patients on ESA therapy may have improved quality of life Use of ESAs may be associated with increased blood pressure and lower *Kt/V* It is difficult to assess the separate impact of ESAs from improved Hb and HCT
rHuEpo in predialysis patients vs. no treatment or placebo	Cochrane Review, 2005, 15 trials, including 461 patients	High for reduction in anemia Moderate for improved quality of life and exercise capacity Low for impact on progression of CKD	rHuEpo was shown to correct anemia and reduce need for blood transfusion Quality of life and exercise capacity also improved in the treatment group	rHuEpo may be used to reduce anemia for people with chronic kidney disease who do not yet require dialysis	Further study is needed to assess whether rHuEpo use can slow the progression of CKD
Epoetin vs. darbopoetin (short-acting vs. long-acting ESAs)	One RCT of 522 HD and PD patients One crossover study of 524 patients with CKD	Low	There is only one RCT currently published which compares darbopoetin and epoetin in the form of RCT. This study shows no statistically significant difference between the two types of ESA. For the crossover study, there was no control group.	There is insufficient evidence to recommend one ESA agent's use over another's	Darbopoetin alfa was found to maintain Hb as effectively as rHuEpo but with a reduced dose frequency for up to 52 weeks in both studies

HCT, hematocrit; IP, intraperitoneal; IV, intravenous; rHuEpo, recombinant human erythropoietin; SC, subcutaneous.
[a] Evidence rating based on study design, study quality, consistency, and directness of results.
[b] Recommendation based on assessment of risks and benefits, quality of evidence, translation of evidence into practice.
[c] Data adapted from [19, 21, 25].
Source: Data adapted from the KDOQ& National Kidney Foundation [24], KDIGO Anemia Workgroup [20], Mikhail et al. [21] recommendations, and Pollock et al. [25].

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Table 64.6 Pediatric studies examining association of ESA dose and Hb level with mortality and morbidity in children on dialysis

References[a]	Type	Population	ESA or Hgb exposure	Sample size	Follow-up	Outcome
Borzych-Duzalka et al. [5]	Prospective cohort	Children and adolescents on chronic PD	Epoetin alfa or beta or darbepoetin alfa administered via SC route only	1394 patients aged 1 month to 20 years	Median follow-up time 0.8 years (IQR 0.22–1.56 years)	Patient survival inversely correlated with ESA dose Patients receiving cumulative weekly ESA doses >6000 IU/m^2 had decreased survival compared with those receiving less
Lestz et al. [76]	Prospective cohort	Prevalent US chronic dialysis patients <18 years • HD data collected October–December 2004 • PD data collected October 2004–March 2005	Epoetin alfa or darbepoetin alfa	829 patients	18 months of mortality data from USRDS	Increased risk of mortality in patients receiving epoetin doses ≥350 units/kg/week or darbepoetin doses ≥1.5 units/kg/week
Dahlinghaus et al. [37]	Prospective cohort	Children on chronic PD aged 0–18 years between October 2004 and March 2005	Epoetin alfa or darbepoetin alfa	468 patients	Hb data linked with 5-year mortality and 4-year hospitalization data from USRDS	Patients with Hb ≥ 11 g/dl were less likely to be hospitalized but no difference in mortality risk compared to those with lower Hb Adjusting for Hb, highest two ESA dosing quartiles were associated with increased risk for hospitalization and death
Rheault et al. [39]	Prospective cohort	Children aged ≤18 years on chronic HD	Hb ≥ 12 g/dl at baseline	1569 patients	Up to 1 year	Hb > 12 g/dl not associated with increased risk for mortality or hospitalization

[a] References listed in reference section.

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evaluate the individual patient's response to ESA treatment and to adjust dosing regimens and frequency of monitoring accordingly.

ESA Dosing

Initial doses and dose adjustments can vary widely in pediatrics. The starting dose of epoetin alfa or beta is generally 20–50 IU/kg three times weekly given either intravenously or subcutaneously, and for darbepoetin alfa is 0.45 μg/kg weekly or 0.75 μg/kg every other week regardless of administration route [20]. ESA dose adjustments after initiation of treatment should generally be done after the first 4 weeks of therapy and no more often than every 2 weeks [20]. When a decrease in Hb is necessary, ESA dose should be decreased but ideally not discontinued, as the pattern of holding and reinitiating therapy may lead to cycling around the desired target Hb range [81]. It should be noted that the dosing requirements for ESA can differ substantially between children and adults. Observational data from the NAPRTCS registry have shown that younger children require higher weight-based rHuEPO doses than adults, ranging from 275–350 U/kg/week for infants to 200–250 U/kg/week for older children [82]. Children and adolescents on HD also require higher absolute doses than adults to maintain target Hb despite lower body weight [4, 83]. Absolute rHuEPO dose of 1000 U given IV to both adults and children can increase Hb by 0.4 g/dl, suggesting that dosing schemes based on Hb deficit rather than on weight may be useful [84]. Differential dose requirements have been noted for CERA agents as well, with children on PD and HD noted to require higher doses to maintain target Hb compared to doses derived from experience with adults receiving CERA [73, 75].

ESA hyporesponsiveness is defined by KDIGO as either no increase in Hb from baseline after the first month of appropriate weight-based dosing or as the requirement for two increases in ESA dose by up to 50% beyond the prior ESA dose at which Hb was previously maintained within goal range [20]. In the IPPN registry, ESA treatment resistance and escalated ESA dosing were associated with inflammation, fluid retention, and hyperparathyroidism [5].

Red Blood Cell Transfusions

Children with treatment-resistant anemia are more likely to require red blood cell transfusions, which are associated with increased risk for development of human leukocyte antigen (HLA) antibodies. In adults, leukoreduction of blood products is an ineffective means to decrease HLA sensitization, and red cell transfusions lead to clinically significant increases in HLA antibody strength and breadth [85, 86]. These antibodies serve as a barrier to future transplantation and may adversely affect graft outcomes [85, 86]. More studies are needed to define the risks associated with red cell transfusion in children with regard to HLA sensitization and graft outcomes.

Monitoring Iron Stores

Iron availability is a rate-limiting step in the maturation of red blood cells, and adequate iron supply is necessary for effective ESA therapy. Assessment of iron stores remains a clinical challenge in patients with CKD, as is distinguishing inflammation-associated impaired iron trafficking from absolute iron deficiency. Transferrin saturation (TSAT) and ferritin are commonly utilized biomarkers of iron available for erythropoiesis and stored iron, respectively, but both have limited sensitivity and specificity to predict bone marrow iron stores and erythropoietic response to iron supplementation [20]. In a cohort of children with nondialysis CKD, ferritin levels ≥100 ng/ml were associated with lower Hb compared to patients with lower serum ferritin, and a TSAT >20% was associated with only a modest increase in Hb [87]. Data from the IPPN registry demonstrates an inverse relationship between Hb and ferritin [5]. In a retrospective cohort study conducted in 45 children on chronic dialysis, reticulocyte Hb equivalent, a measure which reflects iron availability for incorporation into reticulocytes over the preceding 2–4 days, was positively associated with Hb in contrast to ferritin, and more strongly correlated with Hb than TSAT [88]. Unlike ferritin, reticulocyte Hb equivalent is not an acute phase reactant, but is measured by flow cytometry, which limits its availability in clinical practice [88].

Iron Supplementation

Iron may be supplemented enterally or IV. While enteral iron supplementation (dosing range 3–6 mg/kg/day of elemental iron) is relatively inexpensive, highly available, generally safe, and efficacious in many children with CKD, those with more advanced disease or especially those on hemodialysis often benefit from iron preparations administered IV due to poor enteral tolerance or absorption. Table 64.7 summarizes recommendations for iron supplementation in children with CKD. Currently available IV forms of iron supplementation include iron dextran, sodium ferric gluconate, and iron sucrose. There are currently no adequately powered trials comparing IV agents

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Table 64.7 Evidence-based recommendations for iron supplements in CKD

Intervention	Systematic review	Evidence rating[a]	Comment on rating	Recommendation[b]	Comment on recommendation
Initiation of iron supplements		Very low (KDIGO)	Limited studies assessing association of achievement of iron targets with clinical outcomes	For anemic children not on iron or ESA, give oral iron (or IV in HD patients) when TSAT is ≤20% and ferritin is ≤100 ng/ml (KDIGO)	
Definition of iron replete status		Very low (KDIGO) Ungraded (RA)	Limited studies assessing association of achievement of iron targets with clinical outcomes	In children on ESA, give oral iron (or IV in HD patients) to maintain TSAT >20% and ferritin >100 ng/ml (KDIGO) Define iron repletion as % hypochromic red blood cells <6%, reticulocyte Hgb count >29 pg, ferritin >100 ng/ml, TSAT >20% (RA)	Patients should be iron replete to maintain target Hb whether on ESA or not (RA)
			KDOQI: IV vs. PO iron		
IV iron dextran vs. oral iron[c]	Three RCTs: 2 HD patiens, 1 ND patient (two RCTs included placebo arm, one RCT included PD)	Moderately high to high for HD patients	Some inconsistencies for studies which examined ND-CKD patients	The preferred route of iron administration is IV in patients with HD-CKD	Final mean Hb ranged higher 0.9–4.5 g/dl (90–450 g/dl) in IV arms vs. PO for HD patients
IV iron sucrose vs. oral iron[c]	Three RCTs, ND patients	Moderately high for ND and PD patients	Studies in HD patients were reasonably consistent No RCTs with PD patients only	The route of iron administration may be either IV or PO for ND-CKD and PD-CKD patients	Mean final ESA dose was lower in IV arms in studies with HD patients
IV iron sodium gluconate vs. oral iron[d]	One RCT, HD patients				No significant difference in ESA dosing was found in nondialysis patients on IV vs. PO iron

[a] Evidence rating based on study design, study quality, consistency, and directness of results.
[b] Recommendation based on assessment of risks and benefits, quality of evidence, translation of evidence into practice.
[c] Oral iron = ferrous sulfate or iron polysaccharide.
[d] Nondialysis (ND), hemodialysis (HD), peritoneal dialysis (PD).
Source: Adapted from KDIGO Anemia Workgroup [20] and Mikhail et al. [21].

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for adults or children [24]. Several studies comparing IV versus oral iron in adult HD and CKD patients demonstrated superior efficacy of IV forms of iron in repleting iron stores and minimizing ESA dosing [81, 89, 90]. RCT evidence comparing IV versus oral iron in adult CKD, including nondialysis, HD, and peritoneal dialysis patients, is presented in Table 64.7. In 2005, Gillespie and Wolf published a meta-analysis that combined clinical data on IV iron use in children on HD [91]. They included nine studies that included eight cohort studies and one prospective trial with historical controls, and they showed increased Hb, ferritin, and transferrin saturation levels and reduced use of ESAs with IV iron use. In 2004, Warady et al. performed an RCT to examine the preferential route of iron administration for children. The authors prospectively randomized 35 iron-replete children <20 years old with ESRD on HD to receive either IV iron dextran with each dialysis session ($n = 18$) or oral iron daily ($n = 17$) for up to 16 weeks. In both groups the Hb was stable, but the IV iron group experienced a significant increase in serum ferritin and the oral iron group did not. There was no statistically significant difference in ESA dosing detected between the two groups [92].

Concerns about potential adverse effects of IV iron supplementation include increased oxidative stress, iron overload, adverse reactions including anaphylaxis, and increased risk when administered in the context of active infections. There have been no pediatric studies focused on the long-term effects of IV iron supplementation in patients on chronic dialysis. The DRIVE trial, conducted in adults on dialysis, demonstrated that IV ferric gluconate was effective at raising Hb and decreasing ESA dose requirements in patients with ferritin levels 500–1200 ng/ml and TSATs ≤25%, dispelling the widely held belief that patients with ferritin levels in this range were unlikely to benefit from IV iron [93]. However, further study is needed to determine whether IV iron supplementation is effective and safe in children with higher ferritin levels. KDIGO recommends avoidance of IV iron in patients with active systemic infections [20]. Ishida et al. showed, using observational data, that adults on HD who received IV iron within 14 days of hospitalization for a bacterial infection had no increased risk for 30-day or 1-year mortality or readmission or death within 30 days, but no comparable studies have been conducted in children [94]. Goldstein et al. conducted a RCT in 145 children with CKD to compare the safety and efficacy of varying doses of iron sucrose. They showed that a 0.5 mg/kg dose was noninferior to higher dosing regimens (1 and 2 mg/kg) in terms of reaching a composite endpoint of Hb in range of 10.5–14 g/dl, TSAT 20–50%, and a stable ESA dose, supporting the practice of utilizing the lowest effective dose of IV iron in children [95].

There are novel, ESA-independent CKD-related anemia therapies in varying stages of development. Small-molecule hypoxia-inducible factor (HIF) stabilizers/prolyl hydroxylase domain inhibitors modulate HIF-controlled gene products and are capable of inducing endogenous erythropoietin production even in the setting of decreased renal oxygen consumption and have been shown in adult trials to increase Hb and decrease hepcidin, but trials have not been conducted in children [96–98]. Human antihepcidin antibodies have been successfully developed and applied in animal models, but await large-scale trials in humans [99]. Additional iron agents are also under investigation. Ferric pyrophosphate citrate is a novel water-soluble complex iron salt that can be administered via dialysate. It was approved by the FDA in 2015 and has shown good efficacy and safety in adults on hemodialysis, providing smaller amounts of iron over hours which may serve to decrease oxidative stress [100]. Ferric citrate is a novel oral phosphate binder that also supplies elemental iron and has been approved for use in adults [101]. Neither of these novel iron agents have had their safety and efficacy systematically assessed in children as yet.

Conclusions

In summary, anemia is a prevalent and serious problem among children with CKD. At all stages of CKD, low Hb has been associated with increased risk of hospitalization and death, and other comorbidities including decreased QoL. Guidelines for clinical management of anemia in children with CKD are primarily based on adult data. Although the majority of existing pediatric studies do support the current adult guidelines, more pediatric-based research in the form of multicentered RCTs is needed to establish valid pediatric-specific treatment goals. At this time, for children with CKD the treatment goal for anemia management should be a target Hb of ≥11 g/dl and <12 g/dl, using ESAs and iron as necessary adjuncts to achieve this target. Table 64.8 provides a summary of the current treatment guidelines and the certainty and strength of the current evidence.

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Table 64.8 Treatments for anemia in children with CKD

Treatment	Recommendation	Certainty of evidence	Strength of recommendation
Erythropoetic-stimulating agents (short acting) (epoetin alfa, epoetin beta)	Initiation is recommended when Hb ≤10 mg/dl and iron deficiency has been corrected. SC administration is recommended for nondialysis and peritoneal dialysis patients. IV administration is recommended for HD patients. Hb target of 10–12 mg/dl is recommended. Short-acting ESAs are typically given multiple times per week [20].	Moderate	Strong
Erythropoetic-stimulating agents (long acting) (darbepoetin alfa)	Recommendations are the same as for short-acting ESAs, although darbepoietin can be given once every 2 weeks or once monthly [72].	Moderate	Strong
Erythropoetic-stimulating agents (EPO receptor activator – CERA, long acting)	Patients on stable doses of epoetin alfa/beta or darbepoietin may be safely converted to once monthly doses of CERA with no changes to the known safety profile [75]	Moderate	Moderate
rHuEPO vs. darbepoetin	Darbepoietin is considered more patient-friendly than rHuEPO given its less frequent dosing and similar effectiveness [74]	Moderate	Strong
rHuEPO vs. CERA	CERA may be equivalent to rHuEPO in terms of effectiveness and safety profile [75]	Moderate	Moderate
Use of Iron	For anemic children not on iron or ESA, give oral iron (or IV in HD patients) when TSAT is ≤20% and ferritin is ≤100 ng/ml [20]	Low	Strong
Route of iron (use of IV iron vs. PO iron)	PO or IV iron may be used for ND-CKD and PD-CKD patients The preferred route of iron administration is IV for HD-CKD patients [20]	Moderate	Strong

GRADE assessment of the certainty of the evidence(9): High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different* is low. Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different* is moderate. Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different* is high. Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different* is very high. **Substantially different = a large enough difference that it might affect decision-making*.

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65

Peritoneal Dialysis in Children

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Introduction

Peritoneal dialysis (PD) is the most popular chronic dialysis modality in children worldwide. In young children, PD is particularly beneficial because it is fairly simple to perform, it permits home-based therapy, and there is a lower fluid restriction with a more liberal diet than typically occurs with hemodialysis (HD). Despite these apparent benefits, there is no evidence to suggest that PD improves long-term outcomes such as mortality, cardiovascular disease, or metabolic bone disease when compared to HD. Transplantation is the preferred treatment for end-stage renal disease (ESRD) in children, a practice that limits the overall exposure time on dialysis. This lack of exposure time has resulted in a paucity of long-term studies on the outcome of chronic dialysis in children.

A search for available evidence was conducted through The Cochrane Renal Group for Systematic Reviews, the Cochrane Central Register of Controlled Trials, MEDLINE, and EMbase for randomized controlled trials (RCTs) on the management of PD in children(Table 65.1). Recent guidelines on the management of PD in children were also critically reviewed. Data on mortality and comorbidities were obtained directly from annual registry reports and published analyses of these registry data. Studies published before 2000 were predominantly excluded from analysis, unless more recent studies examining a specific topic were not available. Studies examining medications, dietary modifications, and the outcome of predominantly adult patients were excluded from analysis as these topics are covered in other chapters.

PD in Acute Kidney Injury

Acute kidney injury (AKI) is a common complication among hospitalized children and in severe cases renal replacement therapy may be instituted. Despite the common nature of AKI, there are no prospective RCTs comparing the type of renal replacement modality for the treatment of AKI in pediatric patients. Continuous renal replacement therapy (CRRT) is the predominant modality used for children with severe AKI in Europe and the United States, except in young infants [35]; however, PD is still frequently utilized depending upon local center resources and preferences. Retrospective studies with patient selection bias have demonstrated evidence of poorer survival among children treated with PD and CRRT versus HD for the treatment of AKI, but no difference was observed between PD and CRRT [2, 36]. These studies are limited in their significance because older children with a lower severity of illness were predominantly dialyzed using HD in comparison to patients who were dialyzed using PD and CRRT. Current guidelines supporting the use of PD for the treatment of AKI in children have been published, with recommendations largely based on observational studies and expert opinion (Table 65.2) [37, 38].

Numerous retrospective studies and a meta-analysis published in 2018 [39] have demonstrated poor outcomes in hospitalized children with AKI complicated by marked fluid overload. Due to these findings, there has been a growing interest in avoiding a fluid overloaded status through the timely institution of dialysis in patients with AKI. This has been best studied in patients undergoing repair of congenital heart disease. The empiric use of PD following congenital heart surgery has predominantly been studied via

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Table 65.1 Peritoneal dialysis in children.

	Recommendation	Certainty of evidence	Strength of recommendation
Use in AKI	We suggest that PD is an appropriate therapy for management of AKI and fluid overload in pediatric patients. Impact on hard outcomes (mortality, hospital length of stay) is unclear.	Low	Weak [1–5]
Choice of PD modality	We recommend the choice of modality be based upon available resources and physician/family preference. No pediatric-specific studies exist examining hard outcomes and PD modalities. Tidal PD may result in improved clearance, especially in high transporters.	Low	Weak [6, 7]
Dialysis adequacy	We recommend utilizing adult adequacy guidelines as a minimum standard for pediatric patients and making further treatment decisions based on overall patient "wellness." We recommend use of the pediatric modified peritoneal equilibration test to assess peritoneal transport characteristics.	Low	Weak [8–10]
Dialysate choice	We recommend use of neutral-pH, low GDP solutions for PD where available. Lactate and bicarbonate-buffered solutions both provide adequate clearance, with possibly improved membrane preservation with bicarbonate-buffered solutions.	Low	Weak [11–13]
PD catheter placement	We recommend double-cuff Tenckhoff catheters be placed with a lateral/downward tunnel in a paramedian location. The laparoscopic approach is appropriate for PD catheter placement. Omentectomy and fibrin glue application may reduce catheter complications.	Low	Weak [14–21]
Peritonitis diagnosis	We recommend following the current ISPD guidelines for the diagnosis of peritonitis. No pediatric trials exist examining the sensitivity/specificity of current recommended diagnostic criteria for peritonitis. One prospective analysis supports current diagnostic guidelines.	Low	Weak [22, 23]
Peritonitis prevention	We recommend implementation of standardized caregiver education and PD catheter follow-up care bundle to prevent peritonitis. Perioperative antibiotics at PD catheter placement and a "flush-before-fill" system of automated PD are also recommended. Conflicting evidence exists regarding peritonitis prevention with intranasal mupirocin for nasal *Staphylococcus aureus* colonization.	Low	Weak [24–29]
Peritonitis treatment	We recommend following the current ISPD guidelines for treatment of peritonitis. Few pediatric trials exist examining current treatment guidelines, although a prospective evaluation found empiric therapy successful in 93.7% of peritonitis.	Low	Weak [23, 30]
Use in ESRD vs HD	We suggest that PD is an appropriate therapy for management of ESRD. There is currently no strong evidence to support a specific dialysis modality, although there is some suggestion of improved preservation of residual renal function with PD therapy.	Low	Weak [6, 31–33]

AKI, acute kidney injury; ESRD, end-stage renal disease; HD, hemodialysis; ISPD, International Society of Peritoneal Dialysis; PD, peritoneal dialysis. GRADE assessment of the certainty of the evidence [34]: High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different* is low. Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different* is moderate. Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different* is high. Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different* is very high. **Substantially different = a large enough difference that it might affect decision-making*.

retrospective analysis, but appears to be associated with less frequent development of hypervolemia, earlier extubation, and a shorter hospital length of stay [3–5]. There have also been two randomized clinical trials examining the use of PD post cardiac surgery. One demonstrated no difference in achievement of negative fluid balance, time to extubation, or hospital length of stay with PD versus diuretic therapy, but was conducted in a single center and had a very small intervention group that included only 10 patients [40]. The largest randomized trial to date compared PD to furosemide therapy in 73 patients (41 received PD) and demonstrated superior fluid management and shorter ventilator times with PD, but no difference in intensive care unit length of stay, overall hospital length of stay, or mortality [41].

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Table 65.2 Summary of findings: peritoneal dialysis (PD) for acute kidney injury.

Outcome/intervention	No. of participants (no. of studies)	Absolute risk (95% CI)	Relative risk (95% CI)	Certainty of evidence	Conclusion
PD versus diuretics in postcardiac surgery					
Mortality	95 (2)	Assuming baseline risk: 6 per 100; with PD: 4 per 100 (0–9)	0.57 (0.10–3.24)	Low	No clear evidence that PD results in decreased risk of mortality
Negative fluid balance on postoperative day 1	73 (1)	Assuming baseline effect: 66 per 100; with PD: 70 per 100 (57–85)	1.08 (0.78–1.48)	Low	PD may increase the likelihood of achieving a rapid negative fluid balance
Significant fluid overload (10%)	73 (1)	Assuming baseline risk: 43 per 100; with PD: 15 per 100 (4–26)	0.33 (0.15–0.77)	Low	PD may decrease incidence of significant fluid overload
PD versus continuous renal replacement therapy (CRRT) for acute kidney injury					
Mortality	—	No studies	No studies	Absent	No randomized controlled trials comparing PD and CRRT

CI: confidence interval; corresponding risk is the absolute risk for those in the intervention arm or control group.
GRADE assessment of the certainty of the evidence [34]: High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different* is low. Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different* is moderate. Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different* is high. Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different* is very high. **Substantially different = a large enough difference that it might affect decision-making*.

PD for ESRD

Modality of PD

Automated peritoneal dialysis (APD) is the predominant PD modality prescribed for children in nonresource limited countries due in part to the social advantages of nocturnal therapy over daytime PD that are characteristic of continuous ambulatory peritoneal dialysis (CAPD). No studies exist comparing the outcomes of CAPD and continuous cycling peritoneal dialysis (CCPD) in children. During their study of peritoneal membrane characteristics, Fischbach et al. noted that dialysis performed in the supine position, as is the case with CCPD, resulted in ~17% higher transport of creatinine, urea, and phosphate, along with a lower intraperitoneal pressure in comparison to PD conducted in the upright position [42]. There was no difference in net ultrafiltration between the two positions. Edefonti et al. retrospectively examined a group of seven children, all of whom were previously treated with nocturnal intermittent peritoneal dialysis (NIPD) and the absence of a daytime fill volume, and then transitioned to tidal PD, which is characterized by limited complete drains throughout the dialysis session. Increased creatinine and urea clearances were noted in patients undergoing tidal PD, most notably in patients with high peritoneal membrane transport capacity [43]. Holtta et al. compared clearance sequentially in a randomized, crossover trial of 17 patients who underwent both tidal PD and CCPD that demonstrated lower glucose concentration requirements among patients treated with tidal PD and no difference in ultrafiltration [7]. There was a significantly increased dialysate flow rate and creatinine clearance with tidal PD, but no overall difference in Kt/V urea. There was some suggestion of increased clearance in high transporters with tidal PD; however, the small patient population limited statistical evaluation of this difference.

Adequacy of Dialysis and Fill Volume

Determining the optimal dialysis adequacy in children on PD is difficult due to the general rarity of pediatric ESRD, the low incidence of pediatric mortality associated with dialysis treatment of ESRD, and the emphasis on early renal transplantation leading to a relatively short duration of dialysis therapy in most instances. Holtta et al. compared outcomes in an age-matched retrospective analysis of 10 PD patients treated from 1995 to 1999 to 27 patients treated from 1986 to 1995 [8]. In 1995, peritoneal equilibration testing (PET) was added to their treatment program and the target weekly urea Kt/V was increased from 1.7 to >2.0. The analysis demonstrated a significant improvement in anemia and phosphorus control associated with the increased clearance and possible reduction in the number of hospitalization days. Schaefer et al. prospectively examined a cohort of 51 children during an 18-month

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period with a mean Kt/V urea of 2.3 and found that a high transporter state per PET was associated with a high creatinine clearance, but also with poor growth velocity and obesity [9]. At this time, there is no pediatric data to support or refute the current recommendations of a weekly Kt/V urea of >1.8 apart from the studies above, although the guidelines emphasize consideration of patient's overall wellbeing when making treatment decisions [10].

The PD fill volume should be prescribed based upon body surface area (BSA) due to the fact that the peritoneal membrane surface area is independent of age when expressed in terms of BSA. De Boer et al. demonstrated that the association between age and net ultrafiltration disappeared when fill volumes were prescribed as 1200 ml/m^2 BSA instead of 40 ml/kg body weight [44]. Fischbach et al. performed several observational studies that demonstrated no benefit and some decreased clearance with fill volumes over 1400 ml/m^2 BSA [42, 45, 46]. Current guidelines recommend a target fill volume of 1000–1200 ml/m^2 in patients older than 2 years and 600–800 ml/m^2 BSA for younger patients [6, 47]. A small, multicenter study performed by Warady et al. found that solute dialysate to plasma ratios varied with intraperitoneal fill volumes, demonstrating the need for a standardized approach to PET [48]. Warady et al. subsequently performed a multicenter cross-sectional study in which 95 patients underwent a standardized PET and pediatric reference data was generated [49]. This reference data demonstrated that pediatric solute dialysate to plasma ratios are similar to adult data with a standardized fill volume of 1100 ml/m^2; however, age-related changes are present for normalized mass transfer area coefficient (MTAC) with younger children having higher MTAC values.

Dialysate Composition

One of the consequences of long-term PD is the resultant morphological changes to the peritoneal membrane that can lead to decreased clearance and ultrafiltration failure over time. Traditional PD solutions containing glucose as the osmotic agent and lactate as the buffer generate glucose degradation products (GDPs), which result in local and systemic inflammation contributing to these morphological changes [50]. Adult studies have demonstrated mild benefits of "biocompatible" fluids (improved ultrafiltration/clearance) and a Cochrane review found low-quality evidence supporting the use of neutral, low GDP solutions for PD over standard lactate-based solutions [13]. A few trials comparing bicarbonate-buffered PD solutions to standard lactate-buffered solutions have been performed in children [11, 12, 51–53]. These studies have demonstrated improved metabolic acidosis correction, decreased glycation end products, possible improved mesothelial regeneration, and mildly decreased clearance with bicarbonate-based solutions. Schmitt et al. performed a multicenter randomized trial in 37 children on chronic PD comparing lactate-buffered and bicarbonate-buffered neutral-pH dialysate [11]. Following a 2-month run-in period, patients were randomized to either a lactate- or bicarbonate-buffered solution and were monitored via serial visits over the following 10 months. There were no statistical differences in creatinine clearance or Kt/V, but ultrafiltration per glucose exposure significantly increased in association with the use of bicarbonate-buffered solutions and decreased in lactate-buffered solutions. This moderate quality study suggests that use of a bicarbonate-buffered solution is associated with a similar clearance and possibly improved peritoneal membrane preservation when compared to a lactate-buffered PD solution. The study was, however, limited by the small study population, lack of hard outcomes regarding peritoneal preservation, and a short follow-up period.

Amino-acid-based dialysate solutions, which also avoid the risk of GDPs, have historically been proposed for management of protein-calorie malnutrition among children undergoing PD. Few studies have examined these solutions in children and all are complicated by small sample size and relatively short follow-up period [54–56]. No significant benefit was found with regards to anthropometric indices, although the solutions were well-tolerated and there was the suggestion of improved appetite in one study [55].

The use of icodextrin has been studied in several small pediatric studies with several limitations in methodological quality (small sample sizes, lack of randomization, short follow-up period) [57–59]. The largest study of icodextrin use in pediatrics was a retrospective analysis by Rousso et al. which found improved ultrafiltration with fill volumes >550 ml/m^2 (88% achieved any ultrafiltration vs. 44% with fill volumes <550 ml/m^2) [57]. Four patients with possible allergic reactions to icodextrin were reported, although other potential complications of icodextrin therapy were not examined or reported. A crossover study in eight children demonstrated improved clearance (weekly Kt/V increased from 1.99 to 2.54) and increased loss of amino acids with use of icodextrin [58]. Similarly, a crossover trial in 11 children demonstrated equivalent ultrafiltration comparing the use of icodextrin and 3.86% glucose-based solutions [59].

PD Catheter Placement/Usage

In 2012, the International Society of Peritoneal Dialysis (ISPD) published guidelines on PD catheter placement, management, and treatment of peritonitis in children [22]. The majority of these guidelines are supported only by

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expert opinion, with weak evidence. A brief summary of these guidelines is presented in Table 65.3. A double-cuff Tenckhoff catheter with a downward/lateral subcutaneous tunnel is recommended due to decreased rates of infection compared to other catheter characteristics in registry data [14]. However, conflicting results from other registry studies show increased risk of infection with downward tunnels [16, 60]. Para-median catheter placement has been associated with decreased leakage compared to midline placement in one registry study [15]. Catheter tip type (straight vs. curled) has also shown conflicting results with either no significant impact on infection risk [61, 62] or possibly an increased risk for infection/access revision with used of a curled, intraperitoneal segment [63, 64]. Although the potential for a comparative evaluation of double versus single cuff catheters is limited due to the

Table 65.3 ISPD guidelines on initiation of peritoneal dialysis and prevention/treatment of peritonitis in children [22].

PD catheter insertion and care

- Double-cuff Tenckhoff catheter with downward or lateral subcutaneous tunnel
- Perioperative antibiotic prophylaxis
- Weekly sterile dressing changes and catheter immobilization until well-healed
- Use of double-bag and Y-set disconnect systems with "flush before fill"
- Luer-lock connections instead of manual "spiking" of dialysate bags
- Exit-site care with sterile antiseptic solution and topical antibiotic application with dressing changes

Diagnosis of infection

- Peritonitis: cloudy effluent, effluent white blood cells >100/mm^3, >50% polymorphonuclear leukocytes, with or without positive effluent culture
- Exit-site/tunnel Infection: use of exit-site scoring system to assess for swelling, redness, tenderness, or drainage at PD catheter site with or without pathogenic organism isolated by exit-site culture

Treatment of peritonitis

- Intraperitoneal route for empiric initiation of antibiotics when peritonitis is suspected
- Empiric cefepime monotherapy, if indicated and available; otherwise, use first-generation cephalosporin with ceftazidime or aminoglycoside
- If center-specific rates of methicillin resistance are >10%, recommend use of glycopeptide
- Use susceptibility data in guidance of antibiotic selection following culture results
- Duration of intraperitoneal therapy 2–3 weeks depending on microbial species

  Gram-positive organism

  Discontinuation of ceftazidime/aminoglycoside

  If delayed response to therapy (>72 h), recommend addition of rifampin in patients with *Staphylococcus* species

  Gram-negative organism

  Discontinuation of glycopeptide therapy

  Recommend discontinuation of aminoglycoside if possible, once susceptibility data is available

  Suggest administration of second antimicrobial with *Pseudomonas* species

  Culture negative peritonitis

  Empiric antibiotic therapy (other than aminoglycosides) to be continued for 2 weeks

  Recommend discontinuation of aminoglycoside therapy if culture negative with clinical improvement at 72 h

  Fungal

  Recommend catheter removal and treatment with antifungal agent for 2 weeks after catheter removal and resolution of clinical symptoms
- Catheter removal for refractory peritonitis, fungal peritonitis, combined exit-site/tunnel infection and peritonitis with same organism, and refractory tunnel/exit-site infection
- Consider dialysis prescription modification with prolonged dwell time until effluent clears

Treatment of exit-site/tunnel infections

- Oral antibiotic therapy initiated on receipt of culture results unless there is a history of *Staphylococcus aureus* or *Pseudomonas aeruginosa* or signs of severe infection, in which cases empiric therapy is recommended
- Treat for minimum of 2 weeks and at least 7 days after resolution of symptoms except in case of *S. aureus* or *P. aeruginosa* where therapy should be at least 3 weeks

ISPD, International Society of Peritoneal Dialysis; PD, peritoneal dialysis.

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current standard practice of double-cuff catheters in most children (but not all infants), the International Pediatric Peritonitis Registry (IPPR) did find an increased risk of infection with single-cuff catheters [16].

Several retrospective analyses have examined PD catheter complications in children. Rinaldi et al. reported on both 10- and 15-year long-term outcomes from an Italian registry of chronic pediatric PD and found a total 451 catheter complications resulting in an incidence of approximately one catheter complication every 20 months of chronic PD [15, 65]. The most common complications were infection, leakage, catheter dislocation, and catheter obstruction. They found an association between leakage and midline catheter location versus para-median catheter location, although this difference did not reach statistical significance. Catheter complications and catheter removal were more common in young children (<2 years), although this improved in the more recent analysis [15]. An analysis of the International Pediatric Peritoneal Dialysis Network (IPPN) registry found an increased risk of catheter revision/complications in children <1 year of age, those with an ostomy, in countries with higher national GDP, with diagnosis of congenital anomaly of the kidney/urinary tract, and with use of a catheter with a swan-neck tunnel and a curled intraperitoneal portion [63]. Reported indications for catheter revision in the IPPN registry were most commonly mechanical dysfunction/leakage (66%), with peritonitis (16%) and exit/tunnel infection (12%) being less common indications. Similar associations with young age [18, 21, 66–68], ostomy presence [18], and early use [66, 69] have been reported by others.

Due to the risk of leak or necessity for a catheter revision with early catheter use, several studies have reported on the use of fibrin glue to prevent the leakage of dialysate [17, 70, 71]. Sojo et al. performed the only randomized, controlled prospective trial on the utilization of fibrin glue at the time of catheter implantation in 45 children (52 catheter placements) and found a significantly lower rate of leakage (9% catheter leakage in fibrin group, 57% catheter leakage in control group, $P < 0.05$) without any concomitant increase in infection in association with the use of fibrin glue [17]. Laparoscopic placement of PD catheters has become an accepted practice, although no large pediatric trials exist. Several small retrospective studies have found equivalent long-term performance between laparoscopic and open catheter placement in children [18, 19, 21, 72, 73]. Omentectomy at the time of PD catheter placement in children remains somewhat controversial. No large randomized trials examining omentectomy exist and available studies are typically small, single-center, and retrospective in nature. Omentectomy has been found to be associated with less early catheter failure in several small studies [18, 20, 21, 74–76]; however, Radtke et al. found no benefit of omentectomy and found catheter survival dependent more on catheter and surgeon characteristics [68].

PD-associated Infections

Peritonitis and catheter-related infections are the primary cause of catheter removal/revision, morbidity, and treatment failure in children who receive chronic PD. Long-term damage to the peritoneal membrane from infections may lead to peritoneal adhesions/fibrosis and result in the inability to utilize the peritoneal membrane as a dialyzing membrane in the future. Rates of peritonitis, exit-site, and tunnel infections vary depending on the reporting population. Recent publications from registries and collaboratives report a peritonitis frequency of 0.46–0.64 episodes per patient year [14, 62, 77], although rates as low as 0.17 episodes per patient year have been reported [61].

There are no pediatric-specific studies examining the sensitivity or specificity of the diagnostic criteria for peritonitis recommended by the current guidelines (see Table 65.3). A prospective evaluation of the ISPD 2000 guidelines performed by the IPPR found that 3.8% of patients had clear effluent at diagnosis, 2.8% had effluent cell counts <100 cells/μl, and 8.5% of cases had a differential with <50% polymorphonuclear cells [23]. This evaluation included 491 episodes of peritonitis (44% gram-positive, 25% gram-negative, and 31% culture-negative).

Prevention

Preventive strategies for peritonitis and catheter-related infections have been a priority in pediatric studies due to the higher rates of these infections in pediatric (especially young) patients (Table 65.4). The catheter-related preventive strategies discussed above currently do not contradict the current recommendations for a double-cuffed Tenckhoff catheter with a lateral/downward facing tunnel. There have not been any RCTs in pediatrics comparing rates of peritonitis among different PD modalities. Warady et al. completed a prospective randomized multicenter trial of 121 patients which demonstrated that a "flush before fill" APD system was not associated with any impact on overall rates of peritonitis [24]. Nevertheless, gender stratification found significantly lower rates of peritonitis associated with flush before fill in females (one infection every 44.7 months vs. 12.4 months). Due to the lack of an obvious physiological mechanism for a gender difference and the small sample size, further studies are required to confirm this finding. Plastic PD catheter adapters have also been found to be associated with peritonitis in comparison

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Table 65.4 Summary of findings: infection prevention.

Intervention	No. of participants (no. of studies)	Absolute effect (95% CI)	Relative risk (95% CI)	Certainty of evidence	Conclusion
Peritonitis prevention					
Tenckhoff catheter	—	No RCTs	No RCTs	—	No randomized controlled trials comparing Tenckhoff and other catheter types. Registry studies suggest decreased rates of infection.
Downward/lateral subcutaneous tunnel	—	No RCTs	No RCTs	—	No randomized controlled trials comparing catheter placement locations. Registry studies suggest decreased rates of infection.
"Flush before fill"	121 (1)	Assuming baseline risk: 53 per 100; with PD: 40 per 100 (31–50)	0.77 (0.57–1.04)	Very Low	No pediatric evidence that a flush before fill system decreases rates of peritonitis.
SCOPE follow-up bundle	857 (1)[a]	No RCTs	0.49 (0.3–0.8)[b]	Low	Compliance with the SCOPE follow-up bundle likely reduces the subsequent risk of peritonitis.
Exit-site mupirocin	— (1)[c]	—	0.59 (0.46–0.76)	Low	Exit-site mupirocin likely reduces the risk of peritonitis.
Exit-site infection prevention					
10% clorhexidine vs. povidone iodine	150 (1)	Assuming baseline risk: 28 per 100; with chlorhexidine: 5 per 100 (0–10)	0.19 (0.07–0.53)	Low	10% chlorhexidine may be associated with a lower risk of exit-site infections compared to povidone-iodine.
Exit-site mupirocin	—(1)[c]	—	0.43 (0.34–0.54)	Low	Exit-site mupirocin likely reduces the risk of exit-site infection.

CI, confidence interval; RCTs, randomized controlled trials; SCOPE, Standardizing Care to Improve Outcomes in Pediatric ESRD.
GRADE assessment of the certainty of the evidence [34]: High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different* is low. Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different* is moderate. Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different* is high. Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different* is very high. **Substantially different = a large enough difference that it might affect decision-making.*
[a] Analysis of quality improvement study (no randomization or control population).
[b] Multivariate adjusted relative risk.
[c] Systematic review including six studies, number of participants not included in report.

with titanium adapters in univariate analysis, but the finding did not remain statistically significant in multivariable analysis [62].

Survey and registry data have suggested that increased provider/caregiver education and training are associated with lower peritonitis rates [25, 61]. The Children's Hospital Association's Standardizing Care to Improve Outcomes in Pediatric ESRD (SCOPE) Collaborative is a multicenter quality improvement effort designed to improve and standardize practices in pediatric dialysis care [78]. The SCOPE PD catheter care bundles address catheter insertion, patient/caregiver training, and follow-up management and were instituted with a goal of reducing dialysis-related infection. Subsequent analyses of this collaborative have demonstrated that compliance with the follow-up bundle was independently associated with a lower risk of peritonitis, as evidenced by a relative risk (RR) 0.49 (95% confidence interval 0.3–0.8) [62]. Mean monthly peritonitis rates declined from 0.63 episodes per patient year at initiation to 0.42 episodes per patient year at 36 months following implementation of the SCOPE initiative [26]. An analysis of peritonitis rates among patients who received a PD catheter at age <1 year in the SCOPE collaborative found increased rates of peritonitis among patients undergoing nephrectomy at or prior to PD catheter placement (odds ratio [OR] 5.93, 95% confidence interval [CI] 1.51–23.27) and in patients having a gastrostomy placed after PD catheter placement (OR 2.81, 95% CI 1.31–6.01) [64].

Perioperative antibiotics are recommended for prevention of post-catheter placement infectious complications. This

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recommendation is supported by only a single retrospective analysis in pediatric patients that demonstrated a peritonitis rate of 44% in untreated patients versus 10% in those receiving prophylactic antibiotics [79]. A systematic review performed by Van Pierre et al. found that exit-site mupirocin was effective at reducing exit-site infections (RR 0.43, 95% CI 0.34–0.54) and peritonitis (RR 0.59, 95% CI 0.46–0.76) predominantly caused by *Staphylococcus aureus* [27]. No other pediatric studies have been published regarding other topical exit-site antibiotics and adult studies have demonstrated conflicting results [80]. Topical honey has been reported in one pediatric case series of eight patients as being effective in the management of poorly appearing exit-sites, in combination with other treatments [81]. The use of intranasal mupirocin has been associated with conflicting results with some reports of improved prevention of infection [28] versus no impact [29], which is consistent with adult data [80]. This variability may be due to the lack of impact of the therapy on gram-negative infections and the potential development of mupirocin resistance. An RCT of 150 pediatric PD patients demonstrated lower rates of exit site infections (four infections versus 21 infections) with 10% chlorhexidine daily exit-site care compared to povidone-iodine [82].

Treatment

Few trials exist examining treatment of peritonitis in the pediatric population. Available guidelines are based on extrapolated data from adult studies and expert opinion. All experts agree that empiric therapy should consist of broad (gram-positive and gram-negative organisms) coverage, with subsequent therapy to be tailored to the specific organism cultured and the associated antibiotic susceptibilities. Schaefer et al. examined intermittent glycopeptide (every 7 days) and daily ceftazidime versus continuous glycopeptide/ceftazidime intraperitoneal therapy in a prospective randomized trial of pediatric patients [30]. A total of 195 episodes of peritonitis in 90 patients were studied and while no significant difference in treatment outcomes were found, intermittent therapy appeared less successful in the treatment of gram negative peritonitis by clinical judgment, but not by disease severity scores.

The prospective evaluation of the previous pediatric ISPD guidelines (2000) by the IPPR found that there was regional variation in peritonitis and causative organisms, but empiric antibiotics adequately covered 69–97% of bacterial susceptibilities, depending on empiric antibiotic choice [23]. Empiric treatment failure was identified in 6.3% of peritonitis episodes and was associated with gram-negative infections, PD prescription with a "dry" daytime schedule, intermittent ceftazidime administration (gram negative only), and exit-site scores >2 in gram-positive infections.

PD-associated Comorbidities

The presence of comorbidities may have a significant influence on patient outcome, but the evaluation of comorbidities in pediatric PD patients suffers from many limitations. The majority of information regarding comorbidities in pediatric PD comes from registry studies, which are limited by retrospective data, missing/incomplete data, and the voluntary nature of registries. The largest study specifically examining comorbidities in pediatric PD was published in 2012 by the IPPN [83]. They reported on 1830 pediatric PD patients of whom 32.9% had a comorbidity, with cognitive/neurological comorbidities being the most common (15.5% of patients). Motor abnormalities (12.6%), ophthalmologic disease (11.6%), and cardiac disease (9.1%) were the next most common observed comorbidities. These comorbidities were voluntarily reported by treating centers, raising the possibility of incomplete and/or inconsistent data. Other studies have demonstrated high rates of growth retardation, cardiovascular disease, metabolic bone disease, and cognitive impairment in pediatric PD patients [84–87].

PD-associated Patient Survival and Causes of Death

Studies examining pediatric patient survival in association with chronic PD are uncommon due to renal transplantation serving as the definitive treatment for pediatric ESRD. Available evidence is primarily obtained from national and international registries, which invariably results in numerous limitations, including retrospective/incomplete data, inclusion of transplant/HD patients, and lack of data on patients not pursuing therapy for ESRD. Mortality rates among children with ESRD remain significantly increased over the healthy population; however, these rates have been decreasing over time. Registry reports document a mortality rate of 1.5–8.9 per 100 patient years [32, 33, 86, 88–91] or a 5-year survival of 70–91.5% [87, 91–96] over the past two decades for children who receive chronic dialysis. Recent studies typically report a 5-year survival of approximately 90% for children <19 years of age and on PD [97].

Analyses that have focused specifically on the outcomes of neonates and infants initiating renal replacement therapy have demonstrated that significant progress has been made in the survival of the youngest dialysis patients [98–101]. Whereas one study demonstrated no increased risk of death in neonates compared to older infants [98], mortality among infants remains elevated compared to older children [102]. Currently reported 5-year survival among patients who initiated dialysis as neonates ranges from 76.4% to 83.9% [98, 99, 101].

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Determination of the cause of death in children with ESRD is fraught with difficulty. Many registries and studies do not report on the cause of death and the methodology utilized to confirm cause of death is often unclear, with substantial missing data. With recognition of those limitations, most studies have found cardiovascular disease and infection to be the most common causes of death among PD-treated children [14, 31, 33, 88, 92, 93, 98, 101]. Other reported etiologies include malignancy, social (dialysis withdrawal, substance abuse/suicide), and cerebrovascular events [33, 93, 101].

Risk factors and their association with mortality in children on PD are commonly reported, but all studies suffer from the lack of inclusion of children not pursuing renal replacement therapy, transitioning between dialysis modalities, and a short duration of dialysis therapy prior to renal transplantation. Virtually all reports acknowledge young age at onset of dialysis as a primary risk factor for death [32, 33, 86–91, 93–96, 100, 101, 103–105]. With the documented improvement in survival among neonates starting dialysis therapy, there has been an increased frequency of chronic dialysis conducted in relatively sick infants with a variety of comorbidities that also likely impact patient outcome.

PD versus HD

Comparison of outcomes between chronic dialysis modalities is fraught with difficulties due to varying sources of selection bias (e.g. preference for PD in young children, numerous PD modalities). With recognition of those limitations, several registry studies have demonstrated higher mortality rates with PD in comparison to HD [32, 33, 88, 94]. Given the strong association between young age and increased mortality, the association between PD and mortality often fails to persist with multivariate analysis due to the common preference for PD in young children. No RCTs exist comparing risk of death between PD and HD in children. Available registry and cohort studies demonstrate conflicting results. The Dutch National Cohort study demonstrated increased mortality among patients on HD; however, the study suffers from selection bias with more complicated patients receiving HD therapy [87]. An analysis of the European Society of Pediatric Nephrology-European Renal Association (ESPN-ERA)/European Dialysis and Transplant Association (EDTA) registry demonstrated a 6.6-fold increased risk of death with dialysis therapy versus preemptive transplantation, while finding no difference in survival when comparing PD and HD [31].

Residual renal function (RRF) has been found to be an important prognostic indicator for outcomes in adult dialysis patients [106]. While comparable studies associating RRF and definite end-points such as mortality are not available for children, there has been interest in preserving RRF in pediatric patients. Improved linear growth has been associated with the presence of RRF in children receiving PD [107]. Feber et al. demonstrated improved RRF preservation in a retrospective analysis of pediatric PD patients [108]; this finding was also observed in a similar retrospective study was completed by Fissbach et al. in France [109]. An analysis conducted by the IPPN demonstrated evidence of increased risk of RRF loss in PD patients that had either prolonged PD therapy or glomerulonephritis as an underlying etiology of ESRD [110].

Conclusions

PD is a common modality for chronic renal replacement in children. Despite its common use, well-constructed RCTs providing evidence regarding benefits and harms of this therapy are not available. The development of large registries, as well as national and international collaboratives, have greatly improved our understanding of the risks, outcomes, and treatment practices regarding PD in children. Further research with randomized controlled trials based on the observational data that has been generated in pediatric PD should be encouraged.

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66

Hemodialysis

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Introduction

Since the 1960s, when hemodialysis (HD) was first described in children [1], there have been significant technological advances and improvements in the clinical management of children with end-stage kidney disease (ESKD). The availability of portable home hemodialysis (HHD) machines, machines to dialyze premature infants, the encouraging outcomes of using hemodiafiltration (HDF) in children, and extended dialysis programs are some of the medical achievements that have improved the quality of care in the pediatric population with ESKD [2]. Despite these advances, the mortality of children on dialysis remains unacceptably high, and there is no evidence to suggest that HD improves long-term outcomes such as survival, quality of life, cardiovascular disease, or metabolic bone disease when compared to peritoneal dialysis (PD). There are few high-quality randomized studies to provide an evidence base for practice in children on HD. In this chapter, we present the available studies and discuss current clinical recommendations for HD in children.

Literature Search

We searched MEDLINE and EMbase for randomized controlled trials (RCTs), as well as the Cochrane Renal Group for Systematic Reviews, and the Cochrane Central Register of Controlled Trials on the management and outcomes of HD in children. Given that there few RCTs in this field, we performed a wider review of the literature and include prospective observational studies in children (irrespective of the number of patients or duration of study) as well as retrospective studies in children (if >20 children included) and data from international registries describing outcomes in children on chronic dialysis. Studies examining medications, dietary modifications, and the outcome of predominantly adult patients were excluded from analysis as these topics are covered in other chapters.

After critically reviewing the evidence we have followed the Grading of Recommendation, Assessment, Development, and Evaluation (GRADE) [3] method for assessing the certainty of evidence and formulating the strength of recommendations.

Technique of HD, HDF, and Home Dialysis in Children

Conventional HD is characterized by three main principles: diffusion, convention, and ultrafiltration (UF). All forms of extracorporeal dialysis use a semipermeable membrane, which allows only small-to-medium molecular weight (MW) particles to go through, leaving behind larger solutes. Randomized trials in adults suggest that high-flux membranes (with high convection volumes) may be associated with better survival and reduced cardiovascular mortality [4–7]. The main principles and key features of each modality are presented in Table 66.1.

HDF: Potential Advantages Over Conventional HD

Outcomes on dialysis cannot be further improved by increasing the flux or efficiency of HD [8]. HDF utilizes a combination of diffusive and convective solute transport through a highly permeable membrane [9–12], thereby achieving clearance of middle molecular weight solutes unlike conventional HD. In HD circulating uremic toxins

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Table 66.1 Techniques of dialysis.

Technique	Principle	Key features
Hemodialysis	Diffusive small-solute transport that involves the movement of molecules from an area of high concentration to an area of low concentration across a semipermeable membrane	• The dialysis fluid flow and the dialyzer surface area (which determines the mass transfer area coefficient [K_oA] and consequently the solute permeability of the membrane) determine the quality of HD provided
Hemodiafiltration	Combination of diffusion and convection Optimizes the removal of middle (up to 300–500 kDa MW) and larger molecules (>15–50 kDa MW)	• There is no osmotic disequilibrium while arriving at a maximum of the urea clearance (as the continuous iso-osmotic substitution fluid inflow maintains an osmotic stability throughout the whole dialysis session) • The effectiveness of a membrane to ultrafiltrate fluid is described by the UF coefficient (K_{UF}), which is Q_{UF}/delta$P$ (volume of UF per unit time, divided by the pressure gradient across the membrane, the TMP gradient • The FF is the fraction of plasma that is removed from the blood during hemofiltration and the relationship between the TMP and the oncotic pressure determines the FF • In HDF, a high sieving coefficient is required for middle molecule removal
Hemofiltration	Convective transport of small and medium-sized molecules	• It is mainly used in the acute setting in intensive care units, e.g. for rapid fluid removal

FF, filtration fraction; HD, hemodialysis; HDF, hemodiafiltration; MW, molecular weight; TMP, transmembrane pressure gradient UF, ultrafiltration.

such as β2-microglobulin (β2M), retinol-binding protein, adiponectin, leptin, ghrelin, cholecystokinin, cystatin C, and others accumulate and are responsible for systemic inflammation, endothelial dysfunction, and oxidative stress [13, 14]. HDF has been shown to clear significantly more β2M compared to HD [15, 16] and increase removal of inflammatory cytokines with reduction in inflammation and oxidative stress [17]. An observational study in children has shown significant reduction in β2M, inflammatory markers, and measures of oxidative stress and endothelial dysfunction when children were switched from conventional high-flux HD to high volume HDF, keeping all other measures (dialysis time, blood flow speed, filter size, water quality) constant [18].

In adults on dialysis, a recent RCT, the Estudio de Supervivencia de Hemodiafiltración Online (ESHOL) study, has shown a survival benefit of HDF compared to high-flux HD (30% lower risk of all-cause mortality, 33% lower risk of cardiovascular mortality and 55% lower risk of infection-related mortality) [5]. ESHOL, as well as pooled data [7] from the Convective Transport study (CONTRAST) [19], Turkish Online Hemodiafiltration [6] studies, and the French Convective versus Hemodialysis in Elderly (FRENCHIE) study [20] have indicated a critical dose–response relationship between the magnitude of the convection volume and survival. Although a number of biologically plausible explanations have been suggested for improved outcomes with HDF, observational studies, registries, and RCTs provide conflicting results, which to some extent can be explained by differences in the convection volume [7], with patients achieving the highest convection volumes benefiting most. Improved survival and reduced cardiovascular mortality were demonstrated when higher convection volumes (>17.4 and 23 l per session) were used. HDF has been associated with improved cardiovascular outcomes in adults [21], partly explained by improved hemodynamic stability, leading to less intradialytic hypotension and faster recovery time after dialysis [22, 23]. ESHOL, FRENCHIE, and several observational studies have shown that HDF improves intradialytic hemodynamic stability compared to HD [5, 20, 24]. Post hoc analysis of the CONTRAST study, an RCT in adults, showed that HDF helps improve phosphate control (more than 30%) when compared to HD [25]. In addition, patients on HDF compared to HD may have a lower erythropoietin resistance index, possibly associated with reduced inflammation, better biocompatibility, and reduced removal of erythropoietin-inhibiting factors [26].

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The International Pediatric Hemodialysis Network (IPHN) has recently performed a multicenter observational study to test the hypothesis that HDF improves the cardiovascular risk profile, growth and nutritional status, and health-related quality of life outcomes in children compared to conventional HD. The HDF, Hearts and Height (3H Study) [27], the largest pediatric dialysis study to date, suggests an association between HDF modality and lack of progression in vascular measures, increase in height, and self-reported improvement in patient-related outcomes compared to HD. Children on HDF had improved blood pressure and hemodynamic stability, reduced inflammatory markers and lower β2-microglobulin compared to children on HD. The annualized change in vascular measures correlated with improved blood pressure (BP) control and clearances on HDF. 3H is not a randomized trial, so confirmation of results through randomized trials is required.

Smaller pediatric cohorts have previously studied the effects of HDF on nutrition and growth [28], inflammation [18, 29], left ventricular hypertrophy (LVH) [30], anemia control [30], and post-dialysis recovery time [28] but these are single-center and often retrospective case reports. It is postulated that HDF might have a possible anabolic effect associated with the greater removal of uraemic toxins, including hormones that regulate appetite and growth [28]. A small single-center study also suggests that switching children from nocturnal in-center HD to nocturnal in-center HDF has shown significant improvement in BP, phosphate and parathyroid hormone (PTH) control [31]. All potential advantages of HDF over HD are summarized in Table 66.1.

Home Hemodialysis

Literature on pediatric HHD is scarce. The main advantage for children while being on home HD are growth, improved cardiovascular control, and improved quality of life [32]. Improved growth without growth hormone therapy was demonstrated in patients on intensive HD three times a week for approximatively 5 hours per treatment with a single pool Kt/V of 2.0 and a caloric intake at 150% of the recommended daily allowance for age [33].

Simonsen described four children aged 10–19 years who were treated with slow nocturnal HD for 7–8 hours, six nights weekly, for a period of 5–55 months. The children achieved a weekly Kt/V of 7.2–13.6, had no dietary or fluid restriction, and achieved catch-up growth [34].

Hothi et al. studied four children aged between 12 and 16 years on nocturnal HHD with a follow-up period of 6–20 months. All children showed a decrease in their $Ca \times PO_4$ product below 4.4 $mmol^2/l^2$ with a concomitant significant decrease in PTH levels [35]. Review articles from this group suggest that children can be successfully managed with HHD and show many advantages compared to in-center HD, particularly improved appetite, growth, energy levels, increased flexibility with dialysis times, and opportunities to attend school or have a more normal social life [32, 34].

Goldstein et al. have demonstrated improvements in BP control in four patients receiving six-times weekly HHD, with an average of 2.5 hours per treatment for 16 weeks. The dialysis prescription was adjusted to deliver a single-pool Kt/V (spKt/V) ≥2.1. All patients demonstrated progressive reductions in predialysis BP mean values, with progressive discontinuation of antihypertensive medications in two patients [36]. A further case report also suggests that children on home HD can develop regression of LVH and reduced need for antihypertensive treatment [37].

Vascular Access in Children

To optimize dialysis adequacy reliable vascular access is essential. Current HD access options for children include central venous catheters (CVC), arteriovenous fistulas (AVF), and arteriovenous grafts (AVG). The evidence for the benefit of AVFs over CVCs in adult dialysis programs has been known for some time and pediatric studies suggest similar outcomes: better quality dialysis, fewer infections, fewer access changes, and less hospitalization [38–42]. However, AVFs may not be suitable in the very young or those with an anticipated short dialysis course before transplantation, so the "fistula first" policy may not be applicable for all children. Although the international consensus guidelines recommend AVF as the access of choice in children above 20 kg and adolescents who are unlikely to receive a kidney transplant within a year [43–45], most pediatric patients are still dialyzed via a CVC [44–46]. AVGs are used in <2% of children on HD, and usually as a last resort when other options have been exhausted; we have not addressed this further in this chapter [46]. Table 66.2 describes the major outcomes of infections and access patency with CVCs and AVFs.

Central Venous Catheters: Site of Placement

The type and size of catheter, the catheter site, and the technique for insertion need to be considered in order to choose the right catheter for each patient. CVCs in the femoral vein are associated with a higher risk of infections and

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Table 66.2 Summary of evidence for the use of arteriovenous fistula versus central venous catheters in children on hemodialysis.

Outcome	No. of participants (no. of studies)	Summary results from published studies	Certainty of evidence (GRADE)	Conclusion
Infection	198 children (3) [40, 47, 48]	Rate of infection with CVC compared to AVF (0.25 per 100 pm vs. 3.2 per 100 pm) Proportion with infection (1.9% with AVF vs. 16.5% with CVC) Risk relative reduction (34% in AVF group)	Low	Use of AVF for hemodialysis in children may lead to less infection
Access survival and patency	299 children (7) [39, 40, 48–52]	Rate of primary access survival in AVF compared to CVC (1 per 78.8 pm vs. 1 per 15.5 pm) Annualized hospitalization rate of those admitted for access malfunction with AVF compared to CVC (0.44% in AVF vs. 3.1% CVCs) Median survival of AVF compared to CVC (3.14 years [95%CI 1.22–5.06] for AVF, and 0.6 years [95% CI 0.20–1.00] for CVC)	Low	Use of AVF for hemodialysis in children may lead to improved access survival

AVF, arteriovenous fistula; CI, confidence interval; CVC, central venous catheter; pm, patient-months.

thrombosis [53] so should be avoided except in emergency situations or where all other access has failed. Although subclavian catheters are associated with less infectious complications [54], they are clearly associated with a high risk of postoperative stenosis [55], which affects dialysis adequacy and damages the central vasculature, limiting options for future vascular access. A study of 100 patients dialyzed either by a subclavian or internal jugular catheter (50 in each group) showed that 42% of the subclavian group had a stenosis of the subclavian/brachiocephalic vein, compared to 10% of the internal jugular group [56]. Left-sided subclavian and internal jugular catheters provide flows that are more erratic and up to 100 ml/min lower than elsewhere because their tip may abut the vein walls. Although there are no comparative studies in children, a fluoroscopic or ultrasound-guided technique for CVC insertion may be considered to increase the success rate of insertion while decreasing the mechanical complications rate [57, 58]. Recently, the IPHN showed that vascular access dysfunction was more common when the CVC was placed in the femoral (56%) or subclavian vein (35%) as compared to the internal jugular vein (21%, $P = 0.002$) [53].

Arteriovenous Fistulas: Access, Maturation, and Needling

The IPHN registry data suggests that AVFs have better event-free survival probability and thereafter higher primary and secondary patency rates after 1, 2, 3, and 4 years compared to CVCs ($P < 0.0001$ for all time points) [53]. Having a CVC increases the need for new access at a different site by twofold and moreover may compromise fistula formation in the future by causing stenosis and superior vena cava syndrome [45]. In addition, AVFs have been shown to have lower rates of access-related sepsis, reduced frequency of hospitalizations [40], and allow activities that are important to children, such as bathing and swimming (Table 66.2).

However, not every child is a suitable candidate for AVF formation. Using microvascular surgical techniques AVFs can be achieved in small children weighing less than 10 kg [59], but K/DOQI guidelines suggest that an AVF should be given in those weighing more than 20 kg and expected to be listed for >1 year on the kidney transplant list. Given the well-documented benefits of AVF, a recent guideline from the European Society for Pediatric Nephrology (ESPN) dialysis working group suggests AVF formation even for children who are deemed to receive a transplant between 6 months and 1 year [53]. However, for "crash-landers," children being prepared for PD, or children in whom a living donor kidney transplant is planned earlier than 6 months, a CVC might be the appropriate option [53].

Fistulas are needled by the rope ladder or button-hole technique. An AVF in the nondominant arm allows for self-needling of the AVF, easy use of the dominant arm during dialysis, and limits any potential neurovascular complications of surgery to the affected arm. There are no randomized studies comparing different sites of AVF formation in adults or children but pediatric retrospective studies have showed that radiocephalic AVFs have excellent primary and secondary patency rates reaching levels of 78–85% and 94%, respectively [49, 60].

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Outcomes of CVCs versus AVFs in Children

Comparison of AVF versus CVCs in terms of the risk of infection are presented in Table 66.2. The recent clinical practice recommendation for vascular access in children produced by the ESPN presents a comprehensive and up-to-date literature review on the subject [45].

Multiple retrospective studies in children have shown that CVCs present a significant higher infection rate compared to AVFs (Table 66.2). The recent IPHN guidelines reported an overall incidence rate of 1 per 26 catheter months (0.8/1000 catheter days) concerning CVCs, with predominant pathogens thought to be gram-positive (63%), while 17% of blood or exit-site cultures remained negative [53]. Interestingly, De Sousa et al. studied 61 children retrospectively and found that thrombosis is possible and frequent in the pediatric population with AVF, but other studies have shown that choosing the right site for placing an AVF and the use of primary thrombophylaxis decrease the incidence of thrombosis.

In addition to the above, not only were the annual hospitalization rates due to dysfunction were higher for CVCs compared to AVFs, but also the access survival rates were higher for AVFs and a positive overall impact on dialysis adequacy and less anemia episodes was noted with patients dialyzed with AVFs (Table 66.2). Altogether, the higher infection and dysfunction rates of CVCs and the higher survival patency rates with AVFs, places AVF as a better vascular access choice wherever it is possible to perform it.

HD Adequacy

Since the publication of the National Cooperative Dialysis Study in adults in 1981 [61], the efficiency of urea removal has been correlated with patient's morbidity and mortality. Consideration of urea kinetics led to the subsequent mathematical model of Gotch and Sargent, where they propose using Kt/V_{urea} to measure the adequacy of dialysis [62]. Kt/V_{urea} is an estimate of the clearance of urea from the blood during a dialysis session-standardized by total body water (TBW), which reflects the urea distribution volume. Over the years, Kt/V_{urea} has become accepted as the standard measure of delivered dialysis dose used to assess the dialysis adequacy; although the optimum Kt/V for children is not known, it is generally accepted that the delivered dose aimed for in adults should be a minimum in the pediatric population [63].

Although "adequate" dialysis seems to be the target, the pediatric nephrologist is aiming for "optimal" dialysis which includes optimizing nutrition, growth, less need for hospitalization as well as improvement in school attendance and quality of life [64]. When aiming for "optimal dialysis" maximum effort in preservation of the renal residual function (RRF) is critical. RRF can clear uremic toxins that are not removed by conventional dialysis and in adults, even 1 ml/min/1.73 m^2 renal urea clearance is more beneficial than increasing Kt/V by dialysis and is associated with an almost 50% decrease in mortality in adults [65, 66].

Although small solute clearance (represented by urea) is only one part of the effectiveness of dialysis, it is an important and well standardized outcome. We describe the techniques most frequently used to assess adequacy in HD patients:

Urea kinetic model: Urea kinetic modeling is measured by mathematical equations such as the double-pool Kt/V equation, which uses the plasma urea 60 minutes after dialysis in adults, and the single-pool Kt/V (spKt/V), which despite overestimating urea removal is shown to predict mortality in adult studies [67–71]. Goldstein extrapolated and validated an equation in children on HD using the estimated equilibrated blood urea nitrogen (estBUN, from which eKt/V is calculated using a logarithmic extrapolation of the BUN increase from 30 seconds to 15 minutes post dialysis) [72]. Further studies by Mammen et al. demonstrated that a standard Kt/V (stdKt/V) ≥ 2.0 for three-weekly pediatric HD achieves a spKt/V ≥ 1.2 [73]. European guidelines [66] recommend a minimum Kt/V level of 1.2–1.4 and in a more recent study Fischbach et al. suggest a spKt/V > 1.4 in anuric patients [74] to achieve "optimal" dialysis. For simplified Kt/V equations, see to Table 66.3.

The main advantage of kinetically modeled methods for estimating Kt/V_{urea} is that they also provide an estimate of the urea generation rate, from which the normalized protein catabolic rate (nPCR, an estimate of dietary protein intake in the clinically stable patient) can be estimated. However, two of the main drawbacks in this

Table 66.3 *Kt/V* simplified equations.

General formula	$Kt/V = -\log n(R - 0.008t) + (4 - 3.5R)\mathrm{UF}/\mathrm{BW}$
Arteriovenous access	$\mathrm{e}Kt/V = \mathrm{sp}Kt/V - (0.6 \times \mathrm{sp}Kt/V/T) + 0.03$
Venovenous access	$\mathrm{e}Kt/V = \mathrm{sp}Kt/V - (0.47 \times \mathrm{sp}Kt/V/T) + 0.02$

eKt/V, equilibrated Kt/V; R, predialysis urea/postdialysis urea; spKt/V, single-pool Kt/V; UF, weight loss (in kg); t, dialysis time (in hours); V, anthropometric urea distribution volume (in liters).

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model are the possible inaccuracy of the urea clearance (blood recirculation, reduction in the efficacy of dialyzer due to clotting, temporary stop of treatment due to kinked lines/hypotensive patient/other) and the fact that determining the urea distribution volume (V) may be imprecise, especially in children.

1) *Urea reduction ratio*: The urea reduction ratio (URR) has been proposed as another measurement of urea removal during HD. The URR is calculated easily using the percentage of reduction in plasma urea during the dialysis session ($\text{URR} = (1 - \text{urea}_{\text{post}}/\text{urea}_{\text{pre}} \times 100)$). A URR of less than 0.6 has been associated with increased risk of death (odds ratio 1.28 for URRs of 0.55–0.59 and 1.39 for ratios below 0.55) [72]. URR is not recommended as the primary measurement of dialysis adequacy as significant variations of Kt/V may be obtained with each URR value (especially when URR is greater than 0.65) and increasing UF underestimates urea removal. However, it might be a useful assessment in patients with dialysis disequilibrium symptoms.
2) *Measurement of normalized protein catabolic rate (nPCR)*: nPCR is an indirect estimate of protein daily intake ($\text{nPCR} = 5.43 \times G/V + 0.17$), where the urea generation rate (G) is calculated as follows: G (mg/min) = (predialysis BUN × predialysis V) – (postdialysis BUN × postdialysis V)/T, where V is the TBW estimated from 0.58 × body weight and T is time in minutes from the end of the dialysis treatment to the beginning of the next dialysis treatment. Goldstein et al. validated its clinical value [75] by demonstrating that its substantial increase was associated with improvement in nutritional status in pediatric patients with intradialytic parenteral nutrition. However, other studies showed a significant variation in calculated nPCR and underline the underestimation of the prescribed protein intake in that formula [76].

The current guidelines concerning HD adequacy are presented in Table 66.4.

Choice of Anticoagulation in HD/HDF

Prevention of Thrombosis

To prevent circuits clotting with consequent blood loss and reduced dialysis efficacy, anticoagulation of the extracorporeal circuit is almost always required in patients on chronic HD [53]. In the pediatric population, unfractionated heparin (UFH) is primarily used. Concerning UFH, a loading dose of 15–20 units/kg is recommended followed by a continuous infusion of 20–30 units/kg/h and monitoring should include activated partial thromboplastin time (APTT), activated clotting time (ACT), and platelet count on a regular basis. Low-molecular-weight heparin (LMWH) is also used in some centers and is given in divided doses of 0.5–1 mg/kg as the loading dose followed by a half dose in the middle of the dialysis session if the session duration is more than 4 hours in total. Anti-Xa levels should be monitored [77]. Irrespective of which anticoagulant is chosen, the clinician should balance the risk of bleeding versus the risk of clotting. It must be kept in mind that the risk of clotting is inversely related to the dialysis blood flow rate and is higher in less biocompatible dialyzers (e.g. Cuprophane). Whereas LMWH has unpredictable kinetics in ESKD patients, prolonged half-life without any antidote, and an insignificant clearance by HD/HDF as it is impermeable across dialysis membranes, its main benefit is that it consists of a single bolus at the start of dialysis. Comparing the safety and efficacy of LMWH with UFH, meta-analyses show that LMWH seems to be as safe as UFH in terms of bleeding complications and as effective as UFH in preventing extracorporeal circuit thrombosis [78, 79]. A recent Cochrane review showed that tissue plasminogen activator (t-Pa) is the best catheter locking solution in adults on dialysis to prevent catheter thrombosis, reduce risk of bacteremia, and decrease catheter malfunction rates [80]. In maintaining the patency of AVFs or AVGs, a Cochrane review recommends an antiplatelet agent (aspirin, ticlodipine,

Table 66.4 HD adequacy guidelines and recommendations in children.

Guideline	Recommendations	Comments
KDOQI 2015	• sp$Kt/V > 1.4$ • URR > 0.65 (aim at least for 0.70) • Importance of nutritional status (nPCR) and optimize UF	Need for a validated formula to calculate V in children Data extrapolated from adults
European guidelines 2005	e$Kt/V \geq 1.2$–1.4 Importance of nutritional status (nPCR) Monitor growth and cardiac function	Need for a validated formula to calculate V in children Data extrapolated from adults

nPCR, normalized protein catabolic rate; spKt/V, single-pool Kt/V; UF, ultrafiltration; URR, urea reduction ratio.

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or clopidogrel) to be administered for the lifetime of the AVF/AVG [45].

Citrate has the advantage of a regional anticoagulation effect without systemic anticoagulation, but due to the challenges with monitoring and adjusting levels, and the paucity of pediatric experience, it cannot be advised for routine use in chronic HD patients [81] despite its growing application in pediatric plasmapheresis and continuous renal replacement therapy (RRT). In patients with high risk of bleeding, alternative approaches include saline hemodialyzer boluses 60–90 ml/h, optimizing the blood flow depending on the filter, and if the patient is on HDF trying the predilution HDF technique [77].

To prevent CVC malfunction and bacteremia, the only RCT in adults includes 225 patients undergoing HD. The use of heparin three times a week increased the incidence of catheter malfunction (hazard ratio [HR] 1.91, 95% confidence interval [CI] 1.13–3.22, I = 0.02) and catheter-related bacteremia (HR 3.30, 95%CI 1.18–9.22, $P = 0.02$) compared to recombinant tissue plasminogen activator (rt-PA) [82]. In the pediatric population, Gittins et al. conducted a double-blind multiperiod crossover randomized study comparing heparin to alteplase lock in nine children [83] and the main outcome was a 2.4-fold higher risk of clotting when heparin lock is used. In a recent Cochrane review, a combination of antimicrobial and antithrombotic lock solutions did not make any difference to thrombosis compared to the use of standard locking solutions alone [84].

Treatment of Thrombosis

Thrombosis includes both late-onset CVL malfunction (more than 7 days after catheter insertion) and/or fibrin sheath formation (with or without infection). A Cochrane review suggests that thrombolysis with t-Pa should be tried for restoring the CVC patency as it is a safe and effective treatment [85, 86]. Studies in adults suggest that interventional radiology techniques are equal to pharmacological treatment [87] whereas catheter exchange appears to be a superior choice in sheath disruption [88].

Dry Weight and UF Management

At the time of prescribing dialysis, it is important to have assessed the fluid status of the patient, their dry weight, and the desired fluid removal. Prescribing UF allows for the balance of the fluid input and the removal of excessive fluid over time, which serves to make room to maximize nutrition and provide solute clearance by a convective mechanism. Dry weight is the postdialysis session weight at which the patient is considered to be euvolemic and under which the patient will become symptomatically hypotensive. Hypotension is related not only to UF but also to the plasma refilling rate [89]. Incorrect dry weight estimation, with an underestimation of dry weight, can lead to hemodynamic instability, manifesting as hypovolemia-related symptoms or intradialytic hypotension. Defining the dry weight of a child can be very challenging; the physician must account for appropriate growth and changes in body composition, promoting adequate food intake and keeping in mind the largely liquid diet of infants.

Currently, there is no optimal method for assessing the dry weight of a child. Clinical evaluation is the most frequently used method to assess a patient's hydration status. Physical examination for edema, BP measurement, and laboratory parameters such as hemoglobin/hematocrit and serum albumin levels have routinely been used to assess the fluid status of patients on dialysis. Other commonly used techniques include clinical assessment (orthostatic vital signs, jugular venous distention), biochemical markers (e.g. atrial natriuretic peptide [ANP], n-terminal pro brain natriuretic peptide [NTproBNP]), inferior vena cava diameter, bioelectric impedance spectroscopy (BIS), and noninvasive blood volume monitoring markers (Table 66.5). The most commonly used method in children on dialysis is the BIS technique, which estimates the TBW, lean and adipose tissue mass, and overhydration, though scarce data are available on the accuracy of BIS in estimating fluid overload in children on dialysis [93, 103, 104]. In a prospective, observational study in children on dialysis (PD and HD), it was suggested that BIS can serve as an objective method for the assessment of hydration status [90]. In this study, there was a poor correlation between clinical assessment of "dry weight" and BIS-determined weight, with the BIS-determined weight showing a strong correlation with peripheral pulse pressure, higher NTproBNP, and left ventricular end-diastolic diameter. The study also noted a marked discrepancy between BP and hydration status, suggesting that factors other than volume overload may contribute to high BP in some children on dialysis [90]. A further study has shown an improvement in left ventricular mass index (LVMI) and pulmonary edema when BIS was used to guide target weight [94].

Complications of Dialysis

The most serious complications of conventional HD are severe intradialytic hypotension, dialysis disequilibrium syndrome, air embolism, hemolysis during dialysis, and bacteremia/septicemia. Intradialytic hypotension is the

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commonest complication and may be due to multiple patient- and dialysis-related factors, such as difficulty in assessing the dry weight of a patient and targeting higher than required or very rapid UF during the short period of dialysis treatment. Many adult studies have associated intradialytic hypotension episodes with high cardiovascular and all-cause mortality [105]. There are no large studies in children, but a small single-center study has shown that pediatric nocturnal HDF improves the patients' hemodynamic stability [31].

The most common complications in HD patients, and although mild can be extremely distressing for children, are cramps, headaches, nausea, and dialysis-related hypertension. The 3H study reported improved health-related quality of life perceived by children on HDF, but, since the study is not blinded, results must be interpreted with caution [30].

Table 66.5 Summary of findings: dry weight assessment in children.

Method	References	Conclusions	Level of evidence (GRADE)
Biochemical markers	Eng et al. [90] (30 children, longitudinal study, comparison with 13 age-matched healthy controls)	NT-proBNP was significantly elevated when bioimpedance analysis showed overhydration. However, no correlation was seen between NT-proBNP levels and clinical estimation of fluid overload.	Low
Inferior vena cava diameter	Krause et al. [91] (15 children, prospective observational study) Sonmez et al. [92] (12 children, matched-case control study)	Following hemodialysis mean IVCD (average of expiration and inspiration) decreased from 1.12 ± 0.38 to $0.75 \pm 0.26\,cm/m^2$ ($P < 0.0001$). Changes in IVCD were significantly correlated with alterations in body weight following dialysis ($P < 0.0001$). The collapse index (percentage change in IVCD in expiration vs. inspiration) increased significantly after dialysis ($P = 0.035$). IVCD clearly reflected alterations in fluid status. It did not vary significantly with changes in dry weight in a given patient. Increased diameter of the inferior vena cava and plasma ANP concentrations and decreased collapsibility due to overhydration was found. Echography of inferior vena cava may be a promising noninvasive tool to estimate the dry weight in hemodialysis children	Low
Bioelectric impedance study	Eng et al. [90] (30 children, longitudinal study, comparison with 13 age-matched healthy controls) Zaloroszyc et al. [93] (23 children, 1-year retrospective study) Paglialonga F et al. [94] (13 patients on HD 2007 compared to 18 patients on HD 2011, retrospective comparison using the BIS) Brooks et al. [95] (seven children, randomized single-blinded treatment with repeated measurement) Dietel et al. [96] (28 children, prospective study)	BIS provides an accurate assessment of the hydration status and correlates with established biomarkers like NT-proBNP and cardiovascular measures (BP, PWV). Hypertension is not always related to overhydration. Therefore, BIS should restrict the practice of "probing dry weight" in hypertensive children. Moreover, sodium dialytic balance needs to be considered to improve BP management. BIS may be useful in assessing dry weight in pediatric patients on HD. When applying the BIS on patients in 2011, they experienced no pulmonary edema (3/13 patients on 2007 presented four PE episodes). Moreover, when using the BIS patients experienced significantly less LVH and had lower LVMI. Subsequently, by using this tool we can improve patients' cardiovascular status. The use of BIS during HD may aid in the prediction of cardiovascular instability before the development of symptoms because intravascular hypovolemia and hypotension can result from excessive UF below the critical dry weight. In addition, BIA explains, in part, the variability of SBP, DBP, and HR during HD. We suggest that our data also demonstrate the delay in mobilization of fluid from the interstitial space for plasma refill, as evidenced by the delayed change in |Z| over HD. Bioelectric impedance is useful for explaining changes in volemic status and, in part, the variability of SBP, DBP, and HR during HD. Strong correlations of both resistance and IVCD with age, height, weight, and, in particular, body surface area was found. Applying age-related reference intervals to pediatric dialysis patients resulted in overestimation of overhydration.	Low

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Table 66.5 (Continued)

Method	References	Conclusions	Level of evidence (GRADE)
Noninvasive blood volume monitoring (e.g. "Crash" Hct[a])	Michael et al. [97] (nine children, prospective study) Fadel et al. [98] (15 children, prospective study) Patel et al. [99] (20 children, prospective) Candan et al. [100] (nine children, observational study)	Routine determination of target dry weight using NIBVM and aiming for 100% UF helps to achieve the target dry weight, reduces both the risk of chronic fluid overload and the need for antihypertensive medication, and does not lead to increased intra- or interdialytic symptomatology in pediatric patients treated with chronic HD. NIVM can serve as an objective method for determining dry weight as well as predicting and preventing intradialytic morbid events in the pediatric population on maintenance HD. Adoption of a standardized NIBVM-guided algorithm led to (i) improved ABPM profiles, (ii) decreased antihypertensive medication burden, and (iii) decreased UF-associated symptoms. Wider use of NIBVM-guided UF may decrease cardiovascular morbidity in pediatric HD patients. Short-term BVM-guided UF may be a useful tool to diagnose volume overload and to adjust dry weight and, consequently, to achieve a better control of BP in pediatric HD patients.	Low
Lung USS	Allinovi M et al. [101] (23 children, prospective observational study)	Lung ultrasound is a practical and sensitive method of quantifying subclinical fluid overload in infants and children on dialysis.	Low
Air displacement plethysmopgraphy	Wong Vega and Srivaths [102] (15 pediatric and young adult patients, prospective study)	This is the first pediatric dialysis study using ADP to assess body composition. Estimation of FM in pediatric HD patients via ADP and BI has significant error rates in two populations: (i) males with Tanner stage ≥4 (BI underestimates FM) and (ii) weight extremes (BI underestimates FM for obese and overestimates FM for malnourished). BI should be used with caution in these populations when estimating fluid content and leads to false estimates of dry weight.	Low

ABPM, ambulatory blood pressure monitoring; ADP, air displacement plethysmopgraphy; ANP, atrial natriuretic peptide; BI, bioelectrical impedance; BIS, bioelectric impedance study; BP, blood pressure; BVM, blood volume monitoring; DBP, diastolic blood pressure; FM, fat mass; HD, hemodialysis; HR, heart rate; IVCD, inferior vena cava diameter; LVH, left ventricular hypertrophy; LVMI, left ventricular mass index; NIBVM, noninvasive blood volume monitoring; NIVM, noninvasive hematocrit monitoring; NT-proBNP, N-terminal pro-brain natriuretic peptide; PE, pulmonary embolism; PWV, pulse wave velocity; SBP, systolic blood pressure; UF, ultrafiltration. USS, ultrasound scan.
[a] "Crash" Hct is the level of Hct at which the patient has lost more than 10% of his blood volume in 3 hours.

The 3H study showed that patient-related outcome measures that are primarily associated with fluid status, such as the postdialysis recovery time, headaches, dizziness, and cramps, were less frequent and less severe in HDF compared to HD patients. A lower interdialytic weight gain on HDF, implying lower UF rates per session and greater hemodynamic stability, was strongly associated with fewer symptoms. This is supported by the FRENCHIE study, in which fewer symptomatic intradialytic hypotensive episodes and muscle cramps were reported in a vulnerable population of elderly dialysis patients [6]. Similarly, ESHOL reported a lower risk of stroke attributed to improved intradialytic hemodynamic stability in HDF [5, 106]. The Standardized Outcomes in Nephrology – Hemodialysis (SONG-HD) workgroup has identified fatigue as one of the most highly prioritized outcomes for dialysis patients and clinicians [107], and we suggest that it is included in future studies in adults or children on dialysis.

HD in Young Children <10 kg

Neonates and children below 10 kg are very challenging to dialyze for many reasons; vascular access is one of the main issues, as the size of the CVC required may be disproportionally large for the size of the vessels of the neonate/toddler to achieve an adequate blood flow (Poiseuille's law) and usually only single-lumen catheters can be used. The relatively large circuit volume (≥60 ml) implies blood priming to avoid dilution with crystalloid use and anemia in case of circuit loss. For these reasons, PD is usually the modality of choice for

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RRT in infants, but can be fraught with difficulties such as unpredictable UF and less efficient clearance [108]. Currently, the CARPEDIEM device has become available with a miniaturized extracorporeal circuit (27 ml) for babies as small as 2.5 kg and its fluid pump imprecision is ±7.5% [109]. Coulthard et al. have developed the NIDUS machine, which has a circuit volume of 13 ml and can be used in babies weighing as little as 800 g and 3.4 kg, using a single-lumen access line, and without the need for blood priming [110, 111]. The NIDUS generates higher urea, creatinine, and phosphate dialysis clearances than PD, and delivers more precise UF control than either PD or conventional HD [108]. These new machines may allow more precise and safer conventional HD in small children, but more data are needed.

General suggestions based on our experience and the existing literature are:

- **Access in very small children**: Single lumen access may be more appropriate as the lumen of the catheter will be larger and therefore the flow that can be obtained through it is relatively greater. To obtain bidirectional blood flows with a single lumen line, the dialysis circuit has to be modified. This can be achieved by the double-pump method, using two blood pumps which pump alternately, or by using a single pump which pumps intermittently, using gravity to let blood flow back into the child. Disadvantages of the single lumen catheter are that an expansion chamber is necessary in the circuit to allow for the pressure changes and this increases the volume of the blood circuit; dialysis adequacy and clearances are also compromised by a greater degree of recirculation.
- **Anticoagulation**: Tighter control of the degree of anticoagulation can be achieved with lower ACT target ranges, as the increased likelihood of clotting has to be weighed against the detrimental effects of bleeding.
- **HD prescription**: Normally four to five sessions per week are needed in such small children to promote optimal nutrition without restricting the feed volume. Blood priming of the extracorporeal circuit is likely to be needed, and careful attention should be paid to the volume of fluid used for extracorporeal blood replacement at the end of the session.

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67

Urinary Tract Infections in Children

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Introduction

Urinary tract infections (UTIs) are a common and potentially serious infection among children. While most infections are readily treated and do not lead to long-term sequalae, some children go on to develop recurrent infections and/or kidney damage. This chapter reviews the epidemiology of UTIs among children, presentation and treatment of acute infection, risk factors and approaches to managing recurrent infection, the role of diagnostic imaging, and long-term outcomes. Table 67.1 presents recommendations for practice based on the available evidence, which is summarized by topic in Summary of Findings tables throughout the chapter.

Epidemiology

The cumulative incidence of UTIs is around 8% among girls and 2% among boys prior to 7 years of age [2]. The highest risk period for febrile UTIs is the first year of life, when infection is slightly more common among boys, thereafter nonfebrile UTIs among girls predominate [3]. Among boys, circumcision is associated with a substantially lower risk of UTI [4, 5]. *Escherichia coli* (*E. coli*) is the causative organism in about 90% of infections [6, 7]. While there is some fluctuation across time and place, other common causative organisms include *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Enterococcus* species. Infections caused by organisms other than *E. coli* are more common among children with urinary tract abnormalities [8, 9]. Antibiotic resistance is an increasing problem, and more likely among children who have recently received antibiotics [10]. This is reflected globally by a higher prevalence of resistant organisms in countries with a higher rate of antibiotic use among the community, for example where antibiotics are available over the counter [11].

Among children with febrile UTIs, approximately 60% will have renal parenchymal involvement (pyelonephritis), 25% of whom (15% overall) will have residual kidney damage on a follow-up dimercaptosuccinic acid scan (DMSA; otherwise referred to as renal scarring) [12, 13]. The risk of kidney damage is predicted by the severity of initial pyelonephritis as measured by inflammatory markers (neutrophil count, c-reactive protein [CRP]) and temperature, the presence of structural abnormalities on ultrasound, infection with an organism other than *E. coli*, and vesicoureteric reflux (VUR) [13]. Individual patient meta-analysis of 1280 children following a first UTI found that the inclusion of more invasive measures (inflammatory markers, voiding cystourethrogram [VCUG]) added little the predictive ability of a model comprising of only temperature (≥39 °C), ultrasound findings (normal/abnormal), and a causative organism other than *E. coli* [13]. Lower urinary tract dysfunction predicts future kidney damage among children with UTI, probably by increasing the likelihood and frequency of recurrent infections [14].

Between 10% and 20% of children will develop a second UTI in the year following their index infection, with this risk being greatest in the first 3–6 months [15, 16]. A number of risk factors predict recurrence, including the presence of VUR, lower urinary tract dysfunction, and an abnormal renal tract or parenchyma at baseline, with isolated VUR being the least strong predictor, but more important when concurrent with lower urinary tract dysfunction or at higher grades [17].

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Table 67.1 Treatment of urinary tract infection in children.

Treatment	Recommendation	Certainty of evidence	Strength of recommendation
Route of antibiotic delivery	Oral antibiotics are as effective as IV antibiotics in children >1-month old with pyelonephritis. For those too unwell or unable to tolerate oral antibiotics initially, 2–4 days of initial IV therapy is equivalent to 7–14 days.	Moderate (time to resolution of fever, microbiologic cure, recurrence, kidney damage)	Strong
Length of treatment for pyelonephritis	The total length of treatment should be 7–14 days.	Low (microbiologic cure, recurrence)	Weak
Length of treatment for cystitis	A 3- to 7-day course can be used in children with uncomplicated cystitis.	Low (microbiologic cure, recurrence)	Weak
Prophylaxis for recurrent infections	Antibiotic prophylaxis results in small risk reduction for children following an initial UTI (NNT ~ 15 patient-years of antibiotics to prevent one recurrence), but does not reduce kidney damage.	Moderate (recurrence) Low (kidney damage)	Strong
Surgery for vesicoureteric reflux	Given the natural history to improvement with time and negative trial results to date, a watchful waiting approach is appropriate for most patients initially.	Moderate (recurrence, kidney damage)	Strong

CI, confidence interval; IV, intravenous; NNT, number needed to treat.
GRADE assessment of the certainty of the evidence [1]: High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different* is low. Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different* is moderate. Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different* is high. Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different* is very high. **Substantially different = a large enough difference that it might affect decision-making*.

Pathophysiology

Most infections are caused by ascending coliform bacteria, with both host and pathogenic factors contributing to the development and sequalae of UTI. At the pathogen level, the predominance of *E. coli* amongst causative organisms is partly due to the presence of fimbria on most uropathogenic strains [18]. These allow the bacteria to adhere to the uroepithelium in the presence of normal urinary flow, which under normal circumstances acts to displace bacteria within the urinary tract [19]. The host's immune response to infection has been implicated in the pathogenesis of UTI, and several genetic loci linked to innate immunity have been associated with recurrent infection, although heterogeneity among published studies makes it difficult to be certain about the relative importance of individual genes [20]. Another host factor facilitating infection is VUR, which is the retrograde passage of urine from the bladder into the ureter, resulting from an incompetent vesicoureteric valve. As a result, bacteria from the bladder are more easily transferred to the upper urinary tract, potentially leading to pyelonephritis. The vesicoureteric valve is formed at the vesicoureteric junction by the oblique passage of the ureter through the detrusor muscle. VUR is graded from 1–5 according to VCUG findings [21]. Grades 3–5 are associated with progressive dilation of the renal pelvis and calyces, and are often referred to as high-grade, or dilating, reflux. VUR tends to improve with age, as detrusor muscle structure and function matures. Hereditability among families with VUR is well described, but efforts to elucidate the genetic etiology suggest the cause is polygenic and/or the result of complex effect modifiers [22]. Host factors are also important in the development of kidney damage following pyelonephritis. Consistent with its role as one of the key genes regulating fibrosis, transforming growth factor-β1 has been identified as a susceptibility locus [23]. Angiotensin converting enzyme inhibitor polymorphisms may also be important [23]. While both genes are biologically plausible candidates, study quality and heterogeneity limit the certainty of this evidence.

Nonbacterial UTIs can occur (such as fungal, viral), but are uncommon in the immunocompetent host. One notable exception is adenovirus, which may cause a self-limited hemorrhagic cystitis in otherwise well children [24].

Diagnosis

Presentation

Older children with UTIs present in a similar fashion to adult patients. Where infection is limited to the bladder and urethra (cystitis), symptoms may include malodorous

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and/or cloudy urine, dysuria, frequency, urgency, lower abdominal pain, and fever. Infection extending to the kidneys (pyelonephritis) may produce flank pain, and children tend to be more systemically unwell, with vomiting, lethargy, and a high fever.

Young children and infants often have difficulty localizing symptoms. Thus, vague abdominal pain or fever without focus may be the only presenting feature. In combination with the relative frequency of UTIs among children, this makes testing for UTIs mandatory in young children presenting for fever without focus.

Sample Collection

The diagnosis of UTI first requires the collection of an uncontaminated urine sample. In toilet-trained children midstream collection is used, but this is not usually possible for younger children. Bag urine samples are frequently contaminated and are useful in ruling out infection only [25, 26]. Clean catch samples, in–out urethral catherization, and a supra-pubic aspirate are all reliable options [27], although the latter two are more appropriate in children clinically evaluated to be systemically unwell, requiring prompt antibiotic administration. The collection of a clean catch sample may be aided by techniques to encourage voiding. One randomized controlled trial (344 infants) found rubbing cold soaked gauze over the suprapubic region to be effective, resulting in 31% versus 12% of controls voiding within 5 minutes (difference in proportions 19%, 95% confidence interval [CI] 11–28) [28]. Successful supra-pubic aspiration may be aided by bladder scan prior to confirm an adequate quantity of urine in the bladder to readily aspirate. There is widespread practice variation, and the exact approach will also depend on local resources and expertise.

Rapid Diagnostic Testing

The most common rapid diagnostic test is urine dipstick testing for leukocyte esterase and nitrites. Applying an either/or rule for leukocyte esterase (≤ trace) and nitrites, correctly identifies 88% of children with UTI (sensitivity 0.88, 95% CI 0.82–0.91) and conversely a dual negative result makes UTI unlikely. A dual positive result for leukocyte esterase and nitrites is uncommon in children without UTI (specificity 0.98, 95% CI 0.96–0.99). While urine microscopy for white cells is still routinely performed at most centers, leukocyte esterase testing is at least as accurate [29]. Where available, microscopy for bacteria, including gram staining, is the single most accurate test (sensitivity 0.91, 95% CI 0.80–0.96; specificity 0.96, 95% CI 0.92–0.98). However, there is substantial heterogeneity among study results, partly because the relative accuracy of tests varies according to the population sampled (outpatient, inpatient, concurrent bacteremia) and reference standard used (method of collection, culture criteria) [29, 30]. Among some populations, for example where there is a high pretest probability of infection, a clinically relevant number of inaccurate results will be obtained if using rapid diagnostic testing alone.

Microbiologic Criteria

Confirmation of UTI requires the growth of a potentially causative organism from an uncontaminated sample. Both clean-catch and catheter samples may be contaminated during collection, and low-level growth or mixed growth is usually considered to represent contamination. Given urine culture is the current reference standard, it is difficult to establish the accuracy of different culture thresholds and recommendations vary. One approach, based on a review of the literature and expert opinion, is presented in Table 67.2. None of these criteria are absolute, and UTIs have been described at lower thresholds. As with rapid diagnostic testing, interpretation must also depend on the clinical scenario.

While urine culture is the current reference standard, asymptomatic bacteriuria is well described. Cross-sectional screening of 89% of the population of 5–12-year schoolgirls in Cardiff (United Kingdom, 13 369 children) demonstrated a covert bacteriuria prevalence of 1.7% [31]. Furthermore, random allocation of those with bacteriuria to treatment or not had no impact on long-term outcomes. Even among infants, bacteriuria is not uncommon and may have a similar prevalence again [32].

Role of Inflammatory Markers to Identify Pyelonephritis

The utility of CRP, procalcitonin, and the erythrocyte sedimentation (ESR) rate in identifying pyelonephritis among children with febrile UTI has been examined in a Cochrane review (six studies with procalcitonin, 434 children; 13 studies with CRP, 1638 children; six studies with ESR, 1737 children) [33]. This found that a low CRP (<20 mg/l) was the best test to rule out pyelonephritis, reducing the post-test probability to <20%, assuming a pretest probability of 60%. Procalcitonin was the most specific test (summary estimate 0.74, 95% CI 0.55–0.87), and so may be more suited to ruling in infection. While the risk of bias among included studies was low, the certainty around these estimates for specific populations was limited by heterogeneity among included studies.

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Table 67.2 Microbiological criteria for diagnosis of UTI in children.

	Definite UTI[a]		Probable UTI[b]	
Collection method	**No. of organisms (species)**	**CFU/L**	**No. of organisms (species)**	**CFU/L**
Suprapubic bladder tap	1	Any	2	Any
Transurethral catheter	1	$\geq 10^7$	1	$\geq 10^6$
			2	$\geq 10^7$
Voided samples (clean catch, midstream, bag)	1	$\geq 10^8$	1	$\geq 10^7$
			2	$\geq 10^8$

CFU, colony-forming unit(s).
[a] Based on review of 85 studies comparing urine screening tests with urine culture for diagnosis of UTI in children.
[b] Based on consensus opinion of three senior staff specialists in infectious disease, general medicine and nephrology (Children's Hospital at Westmead).

Prognosis

Prospective data suggest that clinically meaningful complications following UTI in children (such as chronic kidney disease or hypertension) without kidney damage at baseline are rare [34]. While new kidney damage on DMSA is often used as a surrogate outcome, this would indicate it is an overly sensitive measure, possibly because most scars involve a relatively small amount of the renal parenchyma and children with previously normal kidneys have adequate renal reserve to compensate for a small reduction in nephron mass.

Historically, kidney damage due to UTI in childhood was thought to be an important cause of end-stage kidney disease (ESKD), and when associated with VUR was labeled reflux nephropathy. However, ESKD due to reflux nephropathy is rare, and many cross-sectional studies likely misclassified cases of renal dysplasia as reflux nephropathy, given testing at a single timepoint cannot reliably differentiate the two [35–37]. That VUR and dysplasia commonly coexist should not be surprising given normal ureteric budding is necessary to induce normal renal development in the developing fetus. The term congenital abnormalities of the kidney and urinary tract (CAKUT) encompasses patients with renal dysplasia and/or concurrent VUR, and better reflects our current understanding of the association between the two [35]. This concept is reflected in registry data, which in recent years, despite a trend to less aggressive management of UTI and VUR, have reported a falling prevalence of ESKD attributed to reflux nephropathy [38, 39]. In contrast, during 1971–1998, when extensive investigation and surgical management of VUR were more common, there was no change in the prevalence of ESKD due to reflux nephropathy [37]. Further to these trends, the low frequency of ESKD due to reflux nephropathy (incidence ~5 per million per year) has never been consistent with clinically relevant kidney disease being common following childhood UTI (prevalence ~5% or 50 000 per million) [37]. In retrospect, a failure to recognize this substantial discrepancy, and a focus on radiologic findings, led to a large number of children being subjected to invasive and unnecessary procedures [40].

Without intervention, the natural history of VUR is resolution with time. Among children enrolled in the Randomized Intervention for Children with Vesicoureteric Reflux (RIVUR) trial, which included 607, <6-year-old children with proven VUR (47% grade 3 or 4), VUR resolved in 51% and was downgraded in a further 23% during 2 years of follow-up [41]. These data are similar to those from other randomized trials for children enrolled in nonoperative intervention or placebo arms [42].

Treatment and Imaging

Acute Infection

Increasingly, the treatment of febrile UTI and pyelonephritis in children is informed by trial-level evidence, with the current Cochrane review including 4452 children from 27 randomized trials [43]. The first set of trials to be performed demonstrated that among children receiving intravenous antibiotics initially there was no difference between a short duration (3–4 days prior to transition to oral antibiotics) and a long duration (7–14 days) of intravenous therapy. This applies equally to symptoms (most commonly measured as time to resolution of fever), proportion of children free of bacteriuria following treatment, and the prevalence of

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persistent renal defects on a 3- to 6-month DMSA scan (Table 67.3) [43]. The next series of trials for pyelonephritis in children investigated whether it was possible to forgo the intravenous component altogether and use only oral antibiotics. These again demonstrated no difference in outcomes between treatment arms (Table 67.4) [43]. Among children receiving intravenous antibiotics initially, the time to resolution of fever was on average 2.05 hours longer (95% CI 0.84 shorter to 4.94 longer) and the relative risk of renal parenchymal defects after 6–12 months 0.82 (95% CI 0.59–1.12). There is still substantial uncertainty around the estimates for kidney damage and in some subgroups of children, such as those with high-grade VUR. The quality of evidence for most findings is moderate, with loss to follow-up (attrition bias) and unclear allocation concealment common among reported trials. Regardless, there are sufficient data on which to make evidence-based suggestions about clinical care (Table 67.1).

There are insufficient head-to-head data to recommend a specific choice of antibiotics, which will be influenced by regional variation in antimicrobial resistance and access to specific agents. The combination of an aminoglycoside to cover gram-negative organisms including *E. coli* and a penicillin to cover *Enterococcus* species, is common. Once-daily aminoglycoside dosing appears as effective and safe as 8-hourly dosing, and although the quality of evidence is low, it seems likely that the large evidence base for once-daily dosing in adults can be translated to children [43].

There are few data to guide the total duration of therapy in children with pyelonephritis, and 7–14 days therapy remains standard practice. However, among children with uncomplicated, lower UTI, it appears the duration of therapy can be safely shortened to 3–5 days (Table 67.5) [44]. The certainty around these estimates for children is low, but the findings are consistent with the large, high-quality evidence base among adults. The current Cochrane review includes four studies (328 children) in the comparison between 3–7 and 7–10 days of antibiotics (Table 67.5) [44]. Another systemic review performed in 2001, with broader inclusion criteria, that included 22 studies (1279 children) found 3 days of therapy equivalent to longer courses [45]. Small studies have considered the efficacy of single-dose therapy, and although the sample sizes are reflected by low precision, persistent bacteriuria was significantly more common (six studies, 228 children, relative risk [RR] 2.01, 95% CI 1.06–3.8). For adults, the extent which antibiotic use in the treatment of cystitis can be minimized has been investigated by randomized trials comparing symptomatic-first and antibiotic-first approaches. These have shown that while it is possible to avoid antibiotics in some patients, around half of those treated symptomatically go on to require treatment. Different authors have interpreted these data differently, either as indicating a failure of symptomatic-first treatment or that symptomatic-first treatment is appropriate for some patients in conjunction with appropriate counseling and a shared decision-making approach [46, 47]. At this point in time there is no evidence to support this strategy in children.

Most trials investigating UTI exclude children less than 1 month of age. One reason for this is a higher rate of bacteremia among young infants, with approximately 10% of

Table 67.3 Summary of findings: short- versus long-course intravenous antibiotics for febrile urinary tract infection.

Outcomes	No. of participants (no. of studies)	Absolute effect (95% CI)	Relative risk (95% CI)	Certainty of evidence (GRADE)	Conclusion
Persistent bacteriuria	305 (4)	Assuming baseline risk 5 per 1000, corresponding risk 4 per 1000 (1–13)	0.78 (0.24–2.55)	Low	Unclear whether longer treatment improves frequency of microbiologic cure
Recurrent infection within 6 months	993 (5)	Assuming baseline risk 59 per 1000, corresponding risk 57 per 1000 (34–95)	0.97 (0.58–1.62)	Moderate	No reduction in recurrent UTI in 6 months following treatment
Persistent kidney damage at 3–6 months	726 (4)	Assuming baseline risk 246 per 1000, corresponding risk 249 per 1000 (197–318)	1.01 (0.8–1.29)	Moderate	No reduction in risk of kidney damage

CI, confidence interval; IV, intravenous.
Corresponding risk is the absolute risk for those in the intervention arm.
GRADE assessment of the certainty of the evidence [1]: High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different* is low. Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different* is moderate. Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different* is high. Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different* is very high. **Substantially different = a large enough difference that it might affect decision-making.*
Source: Based on Strohmeier et al. [43].

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Table 67.4 Summary of findings: all oral versus initial intravenous antibiotics for febrile urinary tract infection.

Outcomes	No. of participants (no. of studies)	Absolute effect (95% CI)	Relative risk (95% CI)	Certainty of evidence (GRADE)	Conclusion
Time to fever resolution (h)	808 (2)	Mean time to fever resolution in intravenous group was 2.05 longer (0.84 shorter to 4.94 longer)		Moderate	Oral and intravenous antibiotics are equally effective at reducing fever
Persistent bacteriuria at 72 h	542 (2)	Assuming baseline risk 5 per 1000, corresponding risk 5 per 1000 (less than 1–87)	1.10 (0.07–17.41)	Low	Imprecise estimate, but no evidence to suggest deviation from equivalence in other outcomes
New kidney damage at 6–12 months	943 (4)	Assuming baseline risk 224 per 1000, corresponding risk 184 per 1000 (132–251)	0.82 (0.59–1.12)	Moderate	It is unlikely that using IV antibiotics initially leads to a meaningful reduction in kidney damage

CI, confidence interval; IV, intravenous.
Corresponding risk is the absolute risk for those in the intervention arm.
GRADE assessment of the certainty of the evidence [1]: High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different* is low. Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different* is moderate. Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different* is high. Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different* is very high. **Substantially different = a large enough difference that it might affect decision-making.*
Source: Based on Strohmeier et al. [43].

Table 67.5 Summary of findings: comparison of 3–7 days of oral antibiotics versus 7–10 days for cystitis.

Outcomes	No. of participants (no. of studies)	Absolute effect (95% CI)	Relative risk (95% CI)	Certainty of evidence (GRADE)	Conclusion
Persistent bacteriuria	265 (2)	Assuming baseline risk 186 per 1000, corresponding risk 205 per 1000 (126–329)	1.10 (0.68–1.77)	Very low	No evidence to suggest deviation from efficacy among adults
Recurrence	363 (4)	Assuming baseline risk 127 per 1000 per 6 months, corresponding risk 145 per 1000 (89–236)	1.14 (0.7–1.86)	Very low	No evidence to suggest deviation from efficacy among adults

CI, confidence interval.
Corresponding risk is the absolute risk for those in the intervention arm.
GRADE assessment of the certainty of the evidence [1]: High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different* is low. Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different* is moderate. Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different* is high. Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different* is very high. **Substantially different = a large enough difference that it might affect decision-making.*
Source: Based on Fitzgerald et al. [44].

children less than 2 months of age having bacteremia at presentation [48]. Hence, it is common practice to initiate treatment with 2–3 days of intravenous antibiotics for young infants with febrile UTI before transitioning to oral antibiotics, provided the child is systemically well and blood cultures are negative. There is variation in the exact threshold applied, but most centers apply a cutoff between 1 and 3 months of age.

Imaging Following Pyelonephritis in Children

The evidence base to guide imaging following pyelonephritis is mostly limited to low-quality, diagnostic test accuracy studies using VUR on VCUG, or kidney damage on DMSA, as the reference standard [49]. Uncertainty about how clinically important either finding is limits the applicability of such studies. A randomized trial of imaging pathways has been performed, but details are limited to the publication

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of one abstract. The trial included 172 2- to 10-year-old children following a first UTI, randomized to routine ultrasound and VCUG, or a selective approach based on recurrent UTI or concerns [49, 50]. There was no difference in UTI recurrence or kidney damage between the arms after 2 years of follow-up, despite 100% of children in the routine arm and 21% of children in the selective arm receiving imaging at some point.

Ultrasound is commonly performed following UTI in children younger than 2–3 years of age. It is a relatively inexpensive, noninvasive procedure that can detect important structural abnormalities, such as posterior urethral valves or severe ureteropelvic junction obstruction, that require surgical intervention [51]. In isolation, ultrasound is not an accurate test for VUR or predictor of subsequent kidney damage [49]. However, the test performance of ultrasound improves substantially when combined with other noninvasive tests [13]. As antenatal ultrasound technology improves, it may be that most children with severe structural urinary tract abnormalities are identified on routine antenatal screening. This would reduce the benefit to performing ultrasound in all children following a first UTI, facilitating a more selective approach to imaging [52].

Nuclear medicine scans are another commonly used imaging modality in childhood UTI. Reduced radioisotope uptake during acute infection signifies pyelonephritis, but rarely changes management [52]. A persistent, new, parenchymal defect following UTI is the reference standard for acquired kidney damage. DMSA provides better cortical resolution than MAG-3, and thus is preferred for this purpose unless obstruction is a specific diagnostic consideration. As discussed previously, most scars detected will not result in clinical sequalae, limiting the clinical utility of routinely performing delayed DMSA. One reason cited for performing delayed DMSA scans in children following UTI is that a normal result makes high-grade VUR highly unlikely [52, 53]. However, a poor specificity (0.44, 95% CI 0.33–0.56) in combination with a low pretest probability of high-grade VUR among most populations will result in a large number of false-positive results, which would require progression to VCUG if detecting high-grade VUR is the primary purpose of the investigation [54]. Assuming a pretest probability of 13%, among 1000 children screened by DMSA for high-grade VUR there will be 487 false-positive results. The relevant Cochrane review includes 10 studies (2499 children), five of which were assessed to be at high risk of bias or reduced applicability, mostly because of patient selection concerns [54]. This was reflected in heterogenous results, leading to low certainty about the findings. However, the results were unchanged when considering only studies at low risk of bias, and no study had a specificity approaching 90%, making it unlikely that the true specificity will be adequate in a population where the pretest probability is low.

VCUG is the reference standard to detect VUR. The test should be delayed until acute infection has resolved, and despite limited evidence many suggest a brief period of antibiotic prophylaxis to prevent procedure-induced infection [55]. It is no longer standard practice to routinely perform VCUG following a first UTI in children. The main reason for this is the low likelihood that a diagnosis of VUR will confer a meaningful change in management, given current evidence suggests that available interventions are highly unlikely to result in a clinically meaningful risk reduction (further discussed in next section). Another reason is that high-grade VUR is uncommon among children presenting with a first UTI, being identified in only 3–4% of cases [7, 13]. The prevalence of high-grade VUR is lower (≤1%) in children with uncomplicated, *E. coli* infections, even among those <3 months old [7]. VCUG is an invasive test, requiring the placement of a urinary catheter and a small ionizing radiation dose [56]. Indirect cystography using a radioisotope such as MAG-3 is appealing as a less invasive method, but the negative predictive value is low and thus utility in reducing formal VCUG limited [49]. VCUG remains an important test in selected cases, for example to detect posterior urethral valves when ultrasound findings indicate obstruction.

Management of Children with Recurrent Infections

There are three main approaches to managing a child with recurrent UTIs: watchful waiting, continuous antibiotic prophylaxis, and surgical correction of VUR when present. Multiple, well-designed, randomized trials have been conducted comparing antibiotic prophylaxis to placebo for the prevention of recurrent UTI. While antibiotics are effective at reducing the incidence of recurrent infections, the effect size is modest (number needed to treat [NNT] is ~15 patient-years of antibiotics to prevent one recurrence) [16, 41]. This must be balanced against an increased proportion of antibiotic-resistant UTI among children on prophylaxis, which may limit the ongoing efficacy of treatment. Since the results of the Cochrane review summarized in Table 67.6, the RIVUR trial has been published [41, 57]. RIVUR demonstrated a similar effect size to previous trials, but among a study population with confirmed VUR (47% grade 3 or 4). The effect size appears constant across sex, age, VUR grade (≤4), and children with a first or second infection. While no individual study has been adequately powered for kidney damage as the primary outcome, a recent systematic review and meta-analysis (seven trials, 1427 children) found no evidence of benefit among the

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Table 67.6 Summary of findings: continuous antibiotic prophylaxis to prevent recurrent urinary tract infections.

Outcomes	No. of participants (no. of studies)	Absolute effect (95% CI)	Relative risk (95% CI)	Certainty of evidence (GRADE)	Conclusion
Recurrence	914 (2)[a]	Assuming baseline risk 150 per 1000 per year, corresponding risk 102 per 1000 per year (72–143)	0.68 (0.48–0.95)	High	Prophylaxis results in a modest risk reduction at a baseline risk of 150 per 1000 children per year
Resistance to prophylactic drug	118 with recurrent infections during trial (2)	Assuming baseline risk 250 per 1000 infections, corresponding risk 600 per 1000 infections (155–2315)	2.4 (0.62–9.26)	Low	Prophylaxis increases the incidence of antibiotic resistant infections[b]

CI, confidence interval.
Corresponding risk is the absolute risk for those in the intervention arm.
GRADE assessment of the certainty of the evidence [1]: High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different* is low. Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different* is moderate. Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different* is high. Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different* is very high. **Substantially different = a large enough difference that it might affect decision-making.*
[a] Studies with adequate allocation concealment.
[b] Small number of patients with recurrent infection, but both well-designed and reported trials, supported by subsequent trial and observational evidence.

cumulative published data (risk ratio 0.83, 95% CI 0.55–1.26) [58]. There is a lack of evidence to guide treatment of children in higher risk subgroups, such as those with a history of frequent UTI or severe hydronephrosis. If the relative effect size among these patients is at least equal to the lower risk populations enrolled in trials to date, then they might derive a substantial risk reduction (absolute effect size) with treatment.

Given high-grade VUR is a predictor of recurrence and parenchymal damage among children presenting with UTI, operative interventions designed to correct VUR have been proposed as a method to improve outcomes among this group of patients. There are two broad categories of intervention, surgical re-implantation of the ureter into the bladder and the endoscopic injection of bulking agents. While intuitively appealing, and previously commonly practiced, it is not clear that operative intervention improves outcomes. One factor favoring the null hypothesis (no effect to intervention) is that the natural history of VUR is improvement over time. Another is that VUR is one of many factors predicting outcomes among children with UTI, and it may be that other factors are relatively more important in determining a patient's clinical course. Compared to no antibiotic prophylaxis alone, endoscopic correction is more likely to result in resolution of VUR after 1–2 years (two studies, 164 children, risk ratio 2.69, 95% CI 1.57–4.63) [59]. In the European arm of the International Reflux Study, surgical correction did not significantly impact VUR status, which is unsurprising given VUR resolved in 299 of 310 ureters among children in the antibiotics-only arm (risk ratio 0.97, 95% CI 0.93–1.00) [59, 60]. Multiple trials have been conducted, but variable methodology and a lack of blinding (bias toward a greater effect size) means there is low certainty about the impact of surgical or endoscopic correction on specific clinical outcomes (Table 67.7) [59]. The available evidence suggests that surgical correction results in a small reduction in febrile UTI by 5 years (equivalent to an NNT of 15), but does not alter the outcomes of symptomatic UTI or kidney damage. Overall, while the certainty about the impact of operative intervention on individual outcomes is low, results consistently indicate that any effect size is small and unlikely to be clinically important. Operative intervention is not without risk, and while some studies report no cases of obstruction, surgical correction resulted in obstruction in 10 of 149 children who received surgery in the European arm of the International Reflux Study [60, 61].

Another important component of treatment that does not usually require pharmacologic or surgical intervention, is the management of lower urinary tract dysfunction, which as discussed is a strong predictor of recurrent infections and kidney damage. Validated questionnaires are available and may improve detection of lower urinary tract dysfunction in clinical settings [62]. Standard therapy for lower urinary tract dysfunction focuses on improving fluid intake and voiding habits. Additional therapies may include bladder training, pelvic floor exercises, biofeedback, and pharmacotherapy aimed at stabilizing detrusor

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Table 67.7 Summary of findings: surgery or endoscopic correction for vesicoureteric reflux versus antibiotic prophylaxis (1–24 months).

Outcomes	No. of participants (no. of studies)	Absolute effect (95% CI)	Relative risk (95% CI)	Certainty of evidence (GRADE)	Conclusion
Symptomatic UTI by 1–2 years (endoscopic correction)	179 (2)	Assuming baseline risk 220 per 1000, corresponding risk 194 per 1000 (57–660)	0.88 (0.26–3.01)	Low	Lack of precision does not rule out benefit to endoscopic correction
Symptomatic UTI by 4–5 years (surgical correction)	393 (1)	Assuming baseline risk 250 per 1000, corresponding risk 238 per 1000 (168–338)	0.95 (0.67–1.35)	Low	Single trial result suggests no reduction in symptomatic UTI with surgical correction
Febrile UTI by 1–2 years (endoscopic correction)	179 (2)	Assuming baseline risk 180 per 1000, corresponding risk 131 per 1000 (27–648)	0.73 (0.15–3.60)	Low	Lack of precision does not rule out benefit to endoscopic correction
Febrile UTI by 5 years (surgical correction)	429 (2)[a]	Assuming baseline risk 200 per 1000, corresponding risk 86 per 1000 (64–140)	0.43 (0.27–0.70)	Low	Surgical correction may reduce febrile UTI by 5 years
New or progressive renal parenchymal defects at 4–5 years (surgical correction)	468 (3)	Assuming baseline risk 422 per 1000, corresponding risk 443 per 1000 (359–544)	1.05 (0.85–1.29)	Low	Available evidence does not support preservation of parenchyma by surgical correction
End-stage kidney disease[b]	154 (2)	Assuming baseline risk 40 per 1000, corresponding risk 40 per 1000 (9–202)	1.07 (0.23–5.04)	Very low	Insufficient evidence to draw conclusion
Hypertension	154 (2)	Assuming baseline risk 60 per 1000, corresponding risk 56 (15–205)	0.93 (0.25–3.42)	Very low	Insufficient evidence to draw conclusion

CI, confidence interval; UTI, urinary tract infection.
Renal parenchymal defects and scars were measure by intravenous pyelogram. Corresponding risk is the absolute risk for those in the intervention arm.
GRADE assessment of the certainty of the evidence [1]: High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different* is low. Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different* is moderate. Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different* is high. Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different* is very high. **Substantially different = a large enough difference that it might affect decision-making.*
[a] The two studies are the European and United States arms of the International Reflux Study, which were considered separately.
[b] Studies included patients with existing parenchymal defects at presentation, possibly due to renal dysplasia.
Source: Based on Nagler et al. [59].

activity. One randomized trial among 6- to 12-year-old children attempted to determine the additive value of oxybutynin (compared to placebo) and bladder training among 97 children with urge incontinence, and pelvic floor training among 105 children with dysfunctional voiding. None of the interventions tested significantly improved the cure rate compared to standard therapy, which was 39% among children with urge incontinence and 52% among children with dysfunctional voiding [63]. Standard therapy in this trial included three visits with a urotherapist, printed summaries of treatment for families, and the use of 72-hour voiding diaries. Another treatment modality sometimes employed for lower urinary tract dysfunction is biofeedback, designed to encourage pelvic floor relaxation during voiding. A recent systematic review found no evidence of benefit to biofeedback, including on the incidence of UTI (four studies, 163 children, odds ratio 1.3, 95% CI 0.65–2.58) [64]. Pharmacologic therapy is sometimes used, including anticholinergic agents and alpha-blockade. Small, heterogenous trials, mostly among children whose primary problem is incontinence, means that there is very low certainty about the efficacy of pharmacotherapy in reducing UTI [65]. Anticholinergic agents, such as oxybutynin and tolterodine, are commonly used. One randomized trial of 62 4- to 12-year-old children with VUR and lower urinary tract dysfunction found that prazosin significantly improved urodynamic parameters and the number of children with improvement in VUR at 12 months compared to placebo (60% versus 17%, risk ratio 0.49, 95% CI 0.32–0.75) [66].

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As discussed, observational data indicate that circumcision is associated with a substantially reduced incidence of UTI in boys [4]. One randomized trial has been conducted among 70 boys presenting with UTI and a normal renal ultrasound, comparing early circumcision (after 3 days) with delay by 6 months (mean age 29 months in early group and 33 months in delayed group) [67]. While circumcision reduced the frequency of bacteriuria in routinely collected samples, there was no significant difference in the number of children with symptomatic UTI, although a low event rate resulted in the trial being underpowered for this outcome (zero versus three infections, risk ratio 0.15, 95% CI 0.01–2.89). There are no randomized data to support routine neonatal circumcision for the primary prevention of UTI [68].

Cranberries and probiotics have been proposed to be effective in preventing and treating UTI, and both treatments have undergone systematic review by Cochrane. Despite promising results among early trials, the cumulative evidence does not support the routine use of cranberries [69]. Among children with recurrent infections, the pooled effect size was greater than other subgroups (two studies, 309 children, risk ratio 0.48, 95% CI 0.19–1.22), but remained nonsignificant. While suggestive of a subgroup effect, it may also simply reflect the smaller sample sizes among studies in children, with smaller studies being prone to inflated estimates of effect [70]. There are fewer data identified regarding the effect of probiotics. For adults and children with recurrent UTI combined, the pooled risk ratio was 0.74 (275 people, four studies, 95% CI 0.54–1.01), but certainty about this estimate is low [71].

Conclusion

UTI is a common childhood infection. While recurrence and kidney damage on DMSA are well described, the best available evidence suggests that with prolonged follow-up, clinically evident kidney disease among children with normal urinary tracts is rare. For most children with pyelonephritis, intravenous antibiotics are unnecessary. The optimal length of treatment for pyelonephritis in children remains unclear, but some data suggest that a shortened course (3–7 days) is adequate for uncomplicated cystitis. Antibiotic prophylaxis reduces the frequency of recurrent infections, but the effect size is modest for children following an initial, or infrequent, UTI. Fewer trials of operative interventions to correct VUR have been conducted, but overall point to a clinically relevant effect size being unlikely, and prospective studies indicate that most children with VUR do well without intervention. The evidence outlined in this chapter is beginning to translate into practice, with fewer admissions for intravenous antibiotics and VCUG being performed [72, 73]. The current evidence base lacks certainty about treatment effects in specific subgroups, and further trials to identify children that might benefit from more aggressive management are in progress.

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Henoch–Schonlein Purpura Glomerulonephritis and IgA Nephropathy in Children

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Introduction

Henoch–Schonlein purpura (HSP) nephritis and IgA nephropathy are the two most common glomerular diseases occurring in children characterized by predominant glomerular IgA deposits. While IgA nephropathy is a renally limited glomerular disorder, HSP nephritis is associated with extrarenal involvement including the typical rash, arthralgia, arthritis, and gastrointestinal involvement. The understanding of the pathophysiology of IgA nephropathy and HSP nephritis, as of now, is identical, with the difference being that IgA nephropathy tends to have an insidious onset, while HSP nephritis occurs and progresses more acutely. Other differences between the two conditions include the peak age of presentation, with HSP nephritis presenting in childhood and IgA nephropathy commonly presenting between the ages of 15 and 30 years [1]. A nephrotic and nephritic presentation also occurs more commonly in HSP nephritis and more endocapillary and extracapillary inflammation is noted on biopsy compared to children with IgA nephropathy [1]. IgA nephropathy more commonly presents with isolated microscopic hematuria or non-nephrotic range proteinuria associated with hematuria [2] and tends to be a slowly progressive disease that occurs sporadically in its most common form, and rarely as a familial disease.

In HSP nephritis, less common manifestations include genitourinary involvement in the form of testicular inflammation, as well as pulmonary and central nervous system involvement. The occurrence of kidney disease is estimated to be as low as 20% in some studies and up to 50% in other studies [3–6]. The renal disease in HSP is quite variable, with the majority of patients demonstrating spontaneous resolution of the nephritis and treatment strategies are based on the risk of progressive disease [4–7]. HSP is a very common disorder in pediatric patients and is less common in adults. However, as described below the development of renal disease associated with HSP is more common and more severe in adolescent and adult patients with HSP compared to the younger patient with HSP [8–14]. Treatment strategies in HSP are based on very few controlled trials with prednisone to prevent the development of renal disease and virtually no controlled trials for therapy of severe renal disease associated with HSP. While there are no controlled trials of therapy for HSP nephritis, there are multiple case series and anecdotal reports of successful immunosuppressive therapy for severe HSP nephritis. Treatment in IgA nephropathy in children is primarily based on adult literature, with a few randomized control trials in children. HSP nephritis and IgA will be discussed in separate sections in this chapter.

HSP Nephritis

Etiology

While the clinical manifestations of HSP are well known, the specific pathogen(s) that triggers the clinical features of HSP is unknown. Associations with group A beta hemolytic strep infections, viral infections including hepatitis B, herpes simplex, human parvovirus B, influenza, and other infections including Toxocara and mycoplasma have been reported by many investigators [15]. HSP has also been associated with a number of drugs, some immunizations, and other agents [15]. The large majority of the reports associating specific infectious agents, drug, or immunizations with

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HSP are anecdotal reports and despite extensive investigation there is no clear pathogen that is accepted as a trigger for the clinical manifestations of HSP. As described below, recent studies suggest genetic susceptibility to the development of HSP and it is also likely that genetic and environmental factors each play a role in the development of HSP and HSP nephritis.

HSP is a leukocytoclastic vasculitis that affects small vessels and the pathology demonstrates white blood cell (WBC) infiltration, small vessels inflammation, and deposition of IgA in vessels obtained from skin biopsies and in the kidney biopsies [16]. IgA containing immune complexes from extrarenal sources result in renal inflammation [16]. In patients who have received a kidney transplant due to end-stage renal disease (ESRD) from HSP nephritis, IgA deposition can reoccur in the transplanted kidney, but this does not typically result in graft failure with the exception of lower graft survival in adults presenting with crescentic nephritis at the time of presentation of HSP [17, 18]. Studies show that abnormalities in the O-linked glycosylation of IgA1 result in abnormal IgA in HSP and in IgA nephropathy [15]. The abnormally glycosylated IgA forms immune complexes with IgG antibodies that are specific to the galactose-deficient abnormal IgA1, which in turn prevents the IgA from being internalized and degraded by liver cells [19, 20]. The abnormal IgA associated immune complexes are deposited in the renal mesangium and trigger the mesangial cells to produce chemokines such as transforming growth factor beta or tumor necrosis factor alpha, which in turn can cause further renal damage [21].

There is no specific test to confirm the diagnosis of HSP and the diagnosis is typically made using the history, physical examination with typical rash, and other clinical manifestations of HSP as described above. In any clinical presentation that is not typical and in severe cases of HSP and HSP nephritis, it is important to rule out other vasculitic diseases such as lupus and ANCA-positive vasculitis with appropriate serologic studies.

Epidemiology of HSP Nephritis

While HSP and HSP nephritis have been described in all age ranges, HSP is most common in children. Age has a major influence on the development of HSP nephritis; multiple studies have demonstrated that the incidence of renal disease in HSP and the severity of the renal disease increases at older ages [22]. A large majority of children with HSP in the first decade of life do not develop serious renal involvement, but the incidence of serious renal disease in the adolescent is increased in comparison to younger children and adults with HSP [9–14].

The incidence of HSP has been reported in several population studies and ranges from 10.45 to 20.4 per 100 000 [23–25]. The incidence of HSP is higher in autumn and winter, and there is a peak amongst children between age of 4 and 6 years of age, with the incidence being as high as 70 cases per 100 000 [4, 23–25]. The incidence of renal involvement in children with HSP is estimated to be around 30–50% [4, 26]. Significant renal involvement manifesting as a nephritic or nephrotic picture is noted in an even smaller percentage of patients and found in about 10–30% of children with renal involvement [4, 26].

In a study of 150 Italian children, the male to female ratio was 1.8 : 1, the mean age was 6.1 years, and renal involvement occurred in 54% with 7% of the children demonstrating severe nephritis and 2% acute renal failure [26].

Several interesting studies have demonstrated that genetic polymorphisms may play a role in the development of HSP and/or in the evolution to HSP nephritis. In a study of 57 patients with HSP, there was no significant difference in the allele or genotype frequencies for two vascular endothelial cell growth factor (VEGF) polymorphisms between patients with HSP and control patients but the high VEGF producer allele was increased in patients with HSP nephritis compared to healthy controls [27]. Polymorphisms of the interleukin-1 beta gene were not different in the patients with HSP compared to controls, but each of the five patients who developed severe nephropathy carried the rare T allele compared with 16 of the remaining 44 patients [28]. The authors suggested that carriage of the interleukin-1 beta T allele influences the severity of renal involvement. Other interesting studies demonstrated that the tubuloglomerular feedback (TGF)-beta C-509T polymorphism of the TGF-beta gene was significantly more common in children with HSP compared to control children [29]. Polymorphisms of the renin-angiotensin system have also been associated with the development of HSP and the possibly the development of renal disease [30]. Patients with familial Mediterranean fever (FMF) have a higher incidence of HSP, with approximately 5% of patients with FMF developing HSP [31]. Similarly, polymorphisms in thrombophilia genes, including methylenetetrahydrofolate reductase, prothrombin, and factor V genes, did not differ in patients with HSP and controls [32]. While more studies clearly need to be performed, it is clear from the existing studies that the development of HSP and the evolution to severe HSP nephritis may be related to genetic susceptibility.

Natural History of HSP Nephritis

HSP nephritis is diagnosed when the patient with HSP develops hematuria with or without proteinuria, nephrotic syndrome, hypertension, and/or decreased renal function

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with elevation of serum creatinine or blood urea nitrogen (BUN). The majority of children with HSP demonstrate mild to no renal disease and when renal disease occurs it usually resolves spontaneously without the need for therapy [3–7].

The majority of patients with HSP who are destined to develop renal involvement will demonstrate renal disease within a few months of the onset of HSP, but unusual cases of the occurrence of HSP nephritis several years after the onset of HSP were reported in the literature [33]. A systematic review has shown that 34.2% of patients who did not have renal involvement at diagnosis subsequently developed renal involvement, and in 85% of cases renal disease developed within 4 weeks, 91% within 6 weeks, and 97% within 6 months [34]. The most common manifestation is hematuria alone, which generally resolves spontaneously and therapy is not required. Some patients also develop proteinuria in addition to hematuria and in the majority of such patients the nephritis will also resolve spontaneously. Proteinuria that is increasing in quantity and/or has evolved into nephrotic syndrome, and/or clinical signs of rapidly progressive glomerulonephritis are highly suggestive of more severe pathology and a worse long-term prognosis. While there are many notable exceptions to this, in general the severity of the clinical presentation and laboratory values correlates with the severity of the pathologic findings [7, 35–38]. Of children who did not have renal disease at presentation, permanent renal impairment did not occur in any child with a normal urinalysis. However, permanent renal damage did occur in 1.6% of children who developed minor urine abnormalities, and 19.5% of those who developed nephritic or nephrotic syndrome developed renal impairment [34].

Evidence for the Efficacy of Therapies in HSPS

Development of Nephritis

Steroids have been used to treat the abdominal symptoms and joint pain of HSP and it has been suggested that steroids may prevent the development of nephritis. Five interventional trials and other retrospective observational studies address this issue [39–43] (Table 68.3). Dudley et al. [94] conducted a randomized, double-blind, placebo-controlled trial to determine if steroids reduce the incidence and severity of nephropathy in HSP. Children <18 years of age (352 participants) were randomized to receive prednisolone 2 mg/kg for 7 days followed by 1 mg/kg for 7 days or placebo for 14 days. The primary outcomes were the presence of proteinuria at 12 months (urine protein to creatinine ratio >20 mg/mmol) and the need for additional treatment (defined by hypertension requiring treatment or renal biopsy abnormalities or the need for treatment of renal disease) during a 12-month follow-up period. No difference was found between those who were randomized to prednisolone compared to the placebo group (adjusted odds ratio for primary outcome 1.29, 95% CI 0.58–2.82, $n = 247$). Another randomized double-blind placebo-controlled trial of 40 children with HSP seen in an emergency room were randomized to receive placebo ($n = 19$) or oral prednisone 2 mg/kg/day for 1 week with weaning of the prednisone over the next week ($n = 21$). At 1 year, there was no difference in the incidence of renal involvement or gastrointestinal complications between the two groups [39]. In a larger study of 171 children with HSP, 84 children were treated with 1 mg/kg/day prednisone for 2 weeks with a tapering dose of prednisone over the next 2 weeks while 87 children received placebo in a

Table 68.1 Treatments for Henoch–Schonlein purpura in children.

Treatment	Recommendation	Certainty of evidence	Strength of recommendation
ACE inhibitors	We suggest that ACE inhibitors be used in children with proteinuria and acute/chronic nephritis for nephroprotection as long as it does not cause significant rise in serum creatinine or potassium	Very low	Weak
Corticosteroids	We suggest the use of corticosteroids either as an IV pulse or oral course as part of the initial treatment in patients with mesangial proliferation, endocapillary proliferation, and/or crescents on kidney biopsy	Low	Weak
Immunosuppression	We recommend the use of additional immune-suppression for 6 months in children with mesangial proliferation, endocapillary proliferation, and/or crescents on kidney biopsy	Very low	Weak
Heparin, warfarin, aspirin or dipyridamole	We do not recommend the use of heparin, warfarin, aspirin or dipyridamole in affected children	Very low	Weak

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double-blind, randomized placebo-controlled trial [40]. In total, 74 patients had renal symptoms (38 in the prednisone group and 36 in the control group) during the 6 months of follow-up. Four patients in the prednisone group and three in the placebo group developed severe nephritis requiring biopsy. Renal symptoms resolved in 61% of prednisone patients after treatment, compared with 34% of the placebo patients ($P = 0.02$). Prednisone did decrease the intensity of abdominal pain and joint pain [40].

Retrospective studies of children with HSP without renal disease at the time of diagnosis demonstrated that prednisone therapy did not decrease the risk of nephritis [42, 48]. However, these studies suggest that prednisone is effective for the joint and gastrointestinal manifestations of HSP but does not prevent the development of renal disease. In contrast, a prospective study of early administration of prednisone (1 mg/kg/day for 2 weeks) in children with HSP and no signs of renal involvement demonstrated that none of the 84 children who received prednisone and 10 of 84 children who did not receive prednisone developed nephropathy within 2–6 weeks after the acute episode of HSP [41].

Altering Course of Established Nephritis

Summary of current recommendations for the treatment of HSP nephritis are listed in Table 68.1. There are very few trials of therapy for established HSP nephritis (Table 68.2). In the study described above by Ronkainen et al., the investigators found that in those who developed renal disease and were treated with prednisone, renal symptoms resolved significantly more rapidly in the prednisone-treated group compared to those in the placebo group [40]. Prednisone therapy was most effective in treating renal disease in patients over the age of 6 who had developed renal symptoms during the first month after the diagnosis of HSP [40].

Table 68.2 Randomized controlled trials in children with HSPN and IgA nephropathy.

Study	Therapy	Number of patients and characteristics	Outcome
Tarshish [44], prospective randomized trial (HSPN)	Supportive therapy with or without 90 mg/m^2/day cyclophosmide	56 children; 28 treated, 28 control	No difference in renal outcome
Ronkainen [40], randomized placebo-controlled (HSPN)	1 mg/kg/day prednisone for 2 weeks and weaning dose for 2 more weeks	84 treated patients and 87 placebo children aged 1.7 to 15.6 years	61% of prednisone-treated renal symptoms resolved 34% of placebo-treated renal symptoms resolved
Yoshikawa [45], randomized controlled (IgA)	Prednisolone[a], azathioprine[b], heparin-warfarin and dipyridamole for 2 years (group 1) vs. heparin-warfarin and dipyridamole only for 2 years (group2)	40 patients in group 1 and 34 patients in group 2 at the time of completion of the trial All patients had diffuse mesangial proliferation on biopsy	Patients in group 1 had less glomerular sclerosis and had less immunological renal injury manifesting as a decrease in mesangial IgA deposits
Yoshikawa [46], randomized controlled trial (IgA)	Prednisone[a], azathioprine[b], heparin-warfarin and dipyridamole for 2 years compared to prednisone alone for 2 years	39 patients received combination therapy and 39 patients received prednisone alone All patients had diffuse mesangial sclerosis	Primary end point: proteinuria <0.1 g/m^2 per day 92.3% of patients in the combination group achieved the primary end point compared to 74.4% in the group receiving prednisone alone Possible increase in sclerotic glomeruli in the group treated with prednisone alone
Hogg [47], double-blind, randomized, placebo-controlled trial	Cellcept vs. placebo after 3-month treatment with lisinopril/losartan and highly purified omega-3 fatty acid	Patients aged 7–70 years with Pr/Cr > 0.6 for males and 0.8 for females and estimated GFR ≥ 50 ml/min/1.73 m^2 or ≥ 40 ml/min/1.73 m^2 if on lisinopril/losartan	No difference in outcomes was noted between the two groups The trial was terminated early at the recommendation of the Data Monitoring Committee due to the absence of any benefit

[a] Prednisone given at 2 mg/kg/day (max. 80 mg/day) for 4 weeks, followed by 2 mg/kg every other day for 4 weeks, 1.5 mg/kg/day every other day for 4 weeks, 1 mg/kg every other day for 21 months.
[b] Azathioprine at a dose of 2mg/kg/day.

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Table 68.3 Evidence for therapy to prevent HSP nephritis

Study	Therapy	Number of patients and patient characteristics	Outcome
Mollica [41], randomized controlled study	1 mg/kg/day prednisone for 2 weeks	84 patients treated with prednisone 84 patients not treated with prednisone (age not reported)	No treated patient developed nephritis 10 (11.9%) control patients developed nephritis
Saulsbury [43], retrospective study	Any prednisone therapy	50 children without nephritis	20% of patients who received predisone and 20% who did not receive prednisone developed nephritis
Islek [42], randomized controlled trial	1 mg/kg/day for 10 days and weaning dose for 1 week	70 patients treated with prednisone and 50 not treated with prednisone aged 9.2 ± 2.7 years	21% (15/70) of treated patients and 36% (18/50) control patients developed nephritis
Huber [39], randomized, placebo-controlled, double-blind trial	2 mg/kg/day prednisone for 1 week and weaning dose for 1 week	21 treated patients and 19 placebo patients aged 2–15 years	No difference in rate of renal involvement 3/21 treated and 2/19 placebo developed nephritis
Ronkainen [40], randomized, placebo-controlled, double-blind trial	1 mg/kg/day prednisone for 2 weeks and weaning for two weeks and weaning dose for 2 more weeks	84 treated patients and 87 placebo children aged 1.7 to 15.6 years	No difference in rate of renal symptoms 38/84 treated and 36/87 control patients had renal symptoms
Bayrakci [48], retrospective study	Prednisone 1 mg/kg PO for 1–2 weeks	157 patients without HSP nephritis	No difference in rate of renal symptoms 17/61 treated patients developed nephritis 18/96 untreated patients developed nephritis
Dudley 2013, randomized, placebo-controlled, double-blind trial	Prednisone 2 mg/kg for 7 days followed by 1 mg/kg for 7 days	352 children randomized	No difference in treated and untreated children

Fifty-six patients participated in a randomized trial of cyclophosphamide and supportive therapy compared to supportive therapy alone (control group); 28 children received supportive therapy and 28 received supportive therapy and cyclophosphamide 90 mg/m^2/day for 42 days [44]. The clinical status at last follow-up (mean follow-up time of 6.93 years) demonstrated that there was no difference in outcome between the two groups. Fourteen of the treated patients and 13 of the control patients were classified as recovered, while 10 of the treated patients and 12 of the control patients were classified as have mild, moderate, or several residual renal abnormalities. Four treated patients and three control patients had reached ESRD. The investigators concluded that therapy with cyclophosphamide was not effective for HSP nephritis. A 12-month, multicenter, prospective, and open-label trial in adults in 2010 compared steroid therapy with steroid and cyclophosphamide cotreatment, with the primary end point being complete remission, and found no benefit of cyclophosphamide [49].

In a study published in abstract form, 19 patients with severe HSP nephritis were treated with cyclosporine A or pulse intravenous methylprednisolone. Ten of 10 (100%) cyclosporine A treated patients compared with five of nine (56%) pulse intravenous methylprednisolone patients achieved remission in 3 months, suggesting that cyclosporine A may be more effective than pulse methylprednisolone in severe HSP. However, this study is quite small and did not have long-term follow-up [50]. Similarly, Jauhola et al. compared cyclosporine treatment for 12 months at a dose of 5 mg/kg with three intravenous methylprednisolone pulses of 30 mg/kg each followed by 4 months of oral prednisone for the treatment of severe HSP nephritis, in a randomized open-label trial [50]. A total of 24 children were in the study. Seven were randomized to receive cyclosporine and eight to receive intravenous methylprednisolone. Four patients were treated with cyclosporine and five with intravenous methylprednisolone without randomization. All 11 patients treated with cyclosporine A had complete remission of nephrotic range proteinuria by 3 months. Six out of 13 children in the intravenous methylprednisolone group did not respond and required additional immune suppressive treatment. However, 2-year biopsies were similar in both groups and both had similar long-term outcomes [50].

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While there is a dearth of evidence-based studies to demonstrate effectiveness of therapy in HSP nephritis, there are numerous retrospective case studies of therapy for HSP nephritis [38, 51–60], but the sum of these is prone to publication bias. In a retrospective study of 12 children with severe HSP nephritis, therapy with pulse intravenous methylprednisolone, oral cyclophosphamide, oral dipyridamole, and oral prednisone resulted in complete remission in seven children, partial remission in four children, and residual nephrotic range proteinuria in one child [51]. In eight children with severe HSP who were treated with pulse intravenous methylprednisolone followed by alternate day prednisone and oral cyclophosphamide daily, seven of the eight patients had a complete remission [52]. In another series, therapy with pulse intravenous methylprednisolone followed by oral prednisone in 38 children resulted in 27 children who recovered normally, seven children had residual renal abnormalities and four children had reached ESRD [53]. In this study, sequential renal biopsies showed a significant decrease of active disease and with a decrease or disappearance of IgA deposits [53]. Among 21 children treated with pulse intravenous methylprednisolone followed by oral prednisone and azathioprine, 19 showed an excellent response to therapy with a decline in hematuria, improvement of renal function, and a marked decrease in proteinuria from 8.8 ± 7.5 g/24 h before therapy to 0.47 ± 0.39 g/24 h after therapy. The remaining two children progressed to ESRD [38]. Of 14 children who were treated with prednisone, cyclophosphamide, heparin/warfarin, and dipyridamole, and were followed for 7.5 ± 0.9 years, nine children demonstrated a complete recovery, four had minor urinary abnormalities and one had residual heavy proteinuria [55]. In this study, histological improvement was also noted in biopsies obtained after the completion of therapy.

When 17 children with severe HSP nephritis who were treated with prednisone 1–2 mg/kg/day and azathioprine 1–2 mg/kg/day were compared to historical controls, significantly more patients in the study group (15 of 17 [88%]) had a favorable outcome compared to the historical control group (17 of 32 [54%]) [54]. At least two retrospective case studies have demonstrated that therapy with cyclosporine A is beneficial in patients with severe HSP [56, 57]. Other therapies including intravenous immunoglobulin therapy, plasmapheresis, and tonsillectomy have been reported in patients resistant to immunosuppressive therapy [58–61].

The paucity of controlled studies of therapy in severe HSP considerably hinders evidence-based recommendations for therapy.

Given the well-described poor outcome of severe HSP nephritis, randomized controlled trials (RCT) comparing placebo to therapy are unlikely to be performed. There is, however, a need to compare different treatment strategies for effectiveness in altering the course of nephritis using low risk of bias study designs. Until such studies are performed, evidence-based treatment recommendations cannot be formulated. Treatment with oral prednisone or intravenous methylprednisolone followed by oral prednisone depending on the severity of nephritis is a reasonable course of action. Since HSP nephritis is a variable disease, individual risk factors for progressive renal disease need to be taken into consideration when formulating therapy for patients with HSP.

IgA Nephropathy

Pathogenesis

IgA nephropathy comprises mesangial deposition of IgA within the glomerulus. Patients with IgA nephropathy overproduce an aberrant form of IgA1. In the aberrant IgA1, there is undergalactosylation of O-glycans at the hinge region along with production of glycan-specific IgG and IgA antibodies against the under galactosylated IgA1 [19]. The level of these serum antibodies in affected individuals has been found to correlate with the degree of proteinuria [19]. The underglycosylated IgA1 molecules can also self-aggregate and form antibody complexes with IgG [19]. In addition, IgG and IgA antibodies that are specific to the hinge region of the abnormal IgA molecule result in the formation of IgA1 immune complexes [62]. IgA deposits are primarily in the mesangium, with limited deposition in the podocytes or tubular epithelial cells. Interactions between cells/molecules in the glomerular region with those in the tubular region may play a role in the tubulointerstitial injury found in patients with IgA nephropathy [63].

There are emerging data demonstrating that the gut–kidney axis, determined by genetics, gut microbes, diet, and the environment, plays a role in the development of IgA nephropathy [64]. In a genome-wide association study, an association between the presence of IgA nephropathy and genes playing a role in immunity against gut pathogens was found [65]. Gene loci involving ITGAM-ITGAX, AVA3, and CARD9 along with two independent signals at HLA-DQB1 and DEFA have been associated with IgA nephropathy and inflammatory bowel disease, maintenance of the intestinal epithelial barrier, and response to mucosal pathogens [65]. Gut microbial diversity also appears to be a factor influencing the development of IgA nephropathy [66]. Compared to patients with IgA nephropathy, healthy controls had the greatest gut microbial diversity. *Enterococcus*, *Lactobacillus*, and

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Clostridium species were found in the highest levels in healthy controls [66]. In contrast, low levels of *Bifidobacterium* species and higher levels of *Streptococceae* were found in patients with IgA nephropathy [66].

There are case reports of celiac disease in patients with IgA nephropathy. Mice that are fed a gluten-rich diet have higher renal IgA deposits compared to mice on a gluten-free diet [67]. In mouse models of IgA nephropathy where the mice are expressing human IgA1 and CD89 (a soluble form of IgA receptor), animals were fed a gluten-free diet for three generations, after which gluten was introduced into their diet for 30 days [68]. After gluten exposure, the mice developed intestinal injury, IgA1 mesangial deposition, increased IgA1-sCD89 complexes, and IgA1-antigliadin antibodies [68]. Proteinuria also increased in the mice [68]. Few studies examining the effect of gluten and IgA nephropathy exist in human subjects exist and they are limited by a small number of patients and a short follow-up. Inferences about the effect of a gluten-free diet in human subjects with IgA nephropathy therefore remain uncertain.

The light microscopy findings on renal biopsy in patients with IgA nephropathy can range from near-normal appearing glomeruli to a rapidly progressing glomerulonephritis picture with cellular crescents. Focal sclerosis without evidence of acute inflammation can also be seen. Mirroring the findings on renal biopsy, patients can present in several different ways, such as with microscopic hematuria alone to rapidly progressing glomerulonephritis or with a nephritic/nephrotic presentation. On immunofluorescence staining for IgA, glomerular deposits of abnormally glycosylated IgA1 are often found diffusely present in the glomerulus [69]. Some patients may also have IgA1 deposits along the capillary walls [69]. Capillary wall deposition of IgA1 has been associated with increased mesangial and endocapillary cellularity and/or advanced fibrosis lending a poorer outcome [70, 71].

Epidemiology and Natural History

The peak age of presentation of IgA nephropathy is between 15 and 30 years [1].

Children do not present before the age of 3 and after that cases are fairly evenly distributed throughout childhood [72, 73]. IgA nephropathy is a slowly progressive condition in most settings and spans the spectrum of childhood into adulthood. Initially it was believed to be a benign condition in children. In long-term studies it appears that in children with hypertension and proteinuria, 10-year renal survival is similar to those of adults and is around 24% [74]. In a retrospective study by Shima et al. among 96 patients having IgA nephropathy with minor glomerular abnormalities that were not treated, 57 patients achieved spontaneous remission by 5 years [75]. However, if all children, even those without hypertension and proteinuria, are included the 10-year survival is significantly better at 87–95% [74, 76]. In children, proteinuria both at presentation and during follow-up is a risk factor for disease progression [77]. Similarly, reduction/resolution of proteinuria during the disease course is a favorable prognostic indicator [78]. Spontaneous remission in children presenting with IgA nephropathy has been observed, while at the other end of the spectrum development of heavy proteinuria can occur in patients who had minimal proteinuria at the time of presentation [75, 79]. Therefore, predicting the course of IgA nephropathy for a single patient based on clinical and biopsy criteria is challenging.

Classification

In 2009 the Oxford Classification for IgA nephropathy was introduced with the goal of providing a common pathological and clinical classification, accepted by the international community, as this would allow for better clinical prognostication and prediction of disease progression in adults and children [80]. Three main pathological lesions were identified to be predictive of renal outcomes: mesangial hypercellularity, segmental sclerosis, and interstitial fibrosis/tubular atrophy [80]. Endocapillary hypercellularity was included as part of the classification because patients with endocapillary proliferation who received immunosuppressive treatment had a significantly lower rate of decline in renal function compared to those who did not, making a case for treatment with immune suppressive medication in patients with such lesions [80]. In the group of patients studied, a 50% reduction in estimated glomerular filtration rate (GFR) as well as rate of renal function decline was associated with increased mesangial hypercellularity, the presence of segmental glomerular sclerosis, and tubular atrophy/interstitial fibrosis [80]. Patients with the greatest degree of tubular atrophy/interstitial fibrosis had the fastest rate of decline in renal function and those with mesangial hypercellularity had the lowest rates of progression [80]. Validation studies in children show that mesangial hypercellularity, endocapillary hypercellularity, and tubular atrophy/interstitial fibrosis are predictors of renal outcome when performing univariate analysis [81, 82]. A large study (161 participants) from China showed that only tubular atrophy/interstitial fibrosis was associated with worse outcomes, while another study from Japan demonstrated mesangial hypercellularity, crescents, and interstitial fibrosis/tubular atrophy to be important variables determining renal outcomes in children [81, 83]. These studies highlight the need to prospectively study a large and diverse pediatric patient cohort.

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A limiting factor in the initial Oxford classification study was that crescents were not included in the classification. This was because a very small number of patients in the study had crescents secondary to exclusion of patients with estimated GFR less than 30 ml/min/1.73 m^2 at the time of biopsy [80]. The 2016 update from the IgA Nephropathy Classification Working Group was published recommending the inclusion of crescents in the classification based on evidence from newer studies showing crescents to be predictive of a worse renal prognosis [84, 85].

Recommendations for Therapy of IgA Nephropathy in Children

Data from several adult studies demonstrates that prednisone therapy slows the progression toward ESRD and also lowers urinary protein excretion [86, 87]. The addition of an angiotensin converting enzyme inhibitor (ACEi) to treatment with corticosteroids improves renal survival [88].

In a RCT of Japanese children, the use of a combination of prednisone, azathioprine, heparin-warfarin, and dipyridamole for 2 years given early in the course of IgA nephropathy decreased the extent of renal injury compared to a 2-year treatment course of just heparin-warfarin and dipyridamole [45]. Kidney injury was confirmed by renal biopsy: the patient had to have an acute presentation with findings of diffuse mesangial proliferation on biopsy. A subsequent analysis assessing the long-term outcomes in this study group after 10 years revealed that based on both univariate and multivariate analysis the 10-year renal survival was better in the children treated with combination therapy that included prednisone and azathioprine [89]. Two out of 40 patients who received combination therapy (5%) developed end-stage kidney disease compared to five of 34 (14.7%) of children who received only heparin-warfarin and dipyridamole. A subsequent randomized trial among Japanese children studied the use of prednisone as a single agent compared to combination therapy (prednisone, azathioprine, heparin-warfarin, and dipyridamole) over 2 years [46]. This study showed that in children with diffuse mesangial proliferation on biopsy the combination therapy was more effective in preventing progressive glomerular sclerosis over the course of 2 years [46]. A recent RCT in 2018 also conducted among Japanese children through the Japanese Pediatric IgA Nephropathy Treatment Study Group compared the effectiveness of prednisone in combination with mizoribine instead of azathioprine (group 1) to a combination of prednisone, mizoribine, warfarin, and dipyridamole (group 2) [90]. The study showed similar rates of remission (give the numbers here for both group for the rates of remission or proportion with remission) in proteinuria between the two groups at the 2-year mark, suggesting that the use of pyridamole and warfarin is unlikely to be of benefit in children [90]. Thirty of 34 patients in group 1 (88.2%) and 27/36 (75%) in group 2 showed normalization of urine protein to creatinine ratio during the 2-year treatment period. According to their study, the disappearance of proteinuria was higher in group 1 compared to group 2 (the group with warfarin and dipyridamole), log-rank $P = 0.04$.

In the adult literature, there are conflicting results from large randomized trials assessing the benefit of the use of mycophenolate mofetil (MMF) in patients with IgA nephropathy with some showing no benefit and others demonstrating improvement in renal function. A recent multicenter, double-blind, RCT of MMF in children and adolescents evaluated the outcomes in children and adults treated with MMF [47]. Patients were initially treated for 3 months with ACEi and purified omega-3 fatty acids and only those patients with persistent proteinuria at the 3-month mark went on to be randomized into the MMF arm or placebo. This trial was terminated early due to lack of benefit as it found no difference between the two groups at the 6-month mark [47]. Another recent trial in adults comparing MMF with low-dose prednisone compared to prednisone alone in patients with active proliferative renal lesions found no difference in renal outcomes between the two groups, but did find less steroid side effects in the group receiving MMF with lower dose prednisone [91]. In a prospective study of eight patients, Roccatello et al. describe significant improvement in patients with acute inflammatory histological lesions and associated significant proteinuria and acute renal insufficiency that were treated with three pulses of intravenous methylprednisolone followed by an oral taper for 4 months along with MMF for 6 months [92]. The authors in this paper speculate that it is patients with acute inflammatory lesions that may benefit the most from treatment with MMF. In 2015, Kang et al. evaluated treatment with MMF in 58 children with nephrotic syndrome associated with IgA nephropathy [93]. Patients were initially treated with prednisone 2 mg/kg/day for 8 weeks. There were 48 children who were steroid resistant, and 33 of these children were then given MMF with a tapering prednisone dose over 4 months. After this 4-month treatment, 21 patients showed complete remission, six patients had partial remission, and six patients did not show any response [93]. Complete remission was defined as urine protein to creatinine ratio of <0.3 g/g and partial remission was defined as >50% reduction in proteinuria from baseline [93]. There were significant differences in renal morphology on biopsy between the steroid-sensitive and steroid-resistant groups, with the steroid-sensitive group having very low MEST (M = mesangial cellularity, E = endocapillary hypercellularity; S = segmental sclerosis, T = tubular

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atrophy) interstitial fibrosis scores as determined by the Oxford Classification. When comparing the group of children demonstrating complete, partial, or no responsiveness to MMF plus prednisone, the children with no response to therapy had a lower GFR at presentation and a higher T score (interstitial fibrosis) [93].

Conclusion

Limited evidence-based recommendations can be made for the treatment of IgA nephropathy and HSP nephritis in children due to overall lack of controlled low risk of bias studies in this population. Nonetheless, based on the studies summarized in this chapter we can conclude that in children with acute and more severe disease with mesangial proliferation and/or nephrotic syndrome, immunosuppression with either oral or intravenous corticosteroids is beneficial. The addition of an ACEi when possible also provides additional benefit for prevention of chronic kidney disease progression. Children with higher MEST scores and mesangial proliferation may benefit from additional treatment with immunosuppressive agents such as azathioprine or MMF for 4–6 months.

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69

Hereditary Nephritis in Children

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Introduction

Hereditary nephritis usually refers to Alport syndrome and thin basement membrane nephropathy, but could also include membranoproliferative glomerulonephritis (dense deposit disease), atypical hemolytic uremic syndrome, and some cases of focal and segmental glomerulosclerosis (FSGS), IgA glomerulonephritis, and systemic lupus erythematosus. All these conditions are associated with hematuria except for FSGS, where proteinuria predominates.

Hematuria occurs in about 6% of the pediatric population [1] and is mainly transient and nonglomerular, from, for example, cystitis or familial hypercalciuria. The most common cause of persistent glomerular hematuria is thin basement membrane nephropathy, and Alport syndrome is much less frequent [1].

Alport Syndrome

Definition

Alport syndrome is an inherited disease characterized by hematuria, progressive kidney failure, hearing loss, and ocular abnormalities [2]. It is suspected when there is hematuria together with a family history of hematuria, kidney failure or Alport syndrome, hearing loss, lamellated glomerular basement membrane (GBM), lenticonus, or a fleck retinopathy [3].

The diagnosis of Alport syndrome is confirmed most accurately with the demonstration of a pathogenic variant in the *COL4A5* gene (with X-linked inheritance) or two variants in the *COL4A3* or *COL4A4* genes (recessive disease) [4–6]. Inheritance is X-linked in 85% of cases and recessive in 15% [7]. The use of "autosomal dominant" inheritance for heterozygous *COL4A3* or *COL4A4* variants remains controversial because the typical Alport features of kidney failure, lamellated GBM, hearing loss, and ocular abnormalities do not occur with single copies of these mutations [6].

Massively parallel sequencing has greatly increased our ability to detect likely causative mutations in Alport syndrome, and identifies the underlying pathogenic variants in nearly 90% of individuals with suspected disease [6]. Whole-exome sequencing has also identified novel combinations of Alport variants, in say *COL4A3* and *COL4A4*, that result in milder features than are typically seen in recessive disease. Conversely, up to 30% of some FSGS cohorts have mutations in the Alport genes and a diagnosis of Alport syndrome [8]. Thus, recent guidelines recommend that genetic testing is used to confirm the diagnosis of Alport syndrome, and that the Alport genes are also included in the panels for FSGS [6, 8].

Epidemiology

In children, Alport syndrome is one of the commonest causes of end-stage kidney failure after FSGS and structural renal disease. In adults, Alport syndrome is second only to polycystic kidney disease as a cause of inherited kidney failure [9].

Reports of the prevalence of Alport syndrome vary from one in 5000 in a well-studied population in Utah [10] to one in 17000 in Southern Sweden [11] and one in 50000 in Finland [12]. However, the abundance of likely pathogenic variants in normal DNA variant databases suggests that Alport syndrome is even more common than one in 5000. Many individuals with X-linked Alport syndrome are undiagnosed, especially boys, men with mild or late onset disease, and girls and women. Indeed, it is only boys and men with the characteristic Alport phenotype who are readily recognized.

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Interestingly, because X-linked inheritance is at least five times more common than recessive disease, overall Alport syndrome occurs nearly twice as often in females as in males, but is usually milder with many fewer women developing kidney failure [13].

Genetics

X-linked Alport syndrome is caused by mutations in the *COL4A5* gene and autosomal recessive disease by two *COL4A3* or *COL4A4* mutations. Features are similar in boys with X-linked disease, and boys and girls with recessive inheritance. Thin basement membrane nephropathy occurs with a heterozygous *COL4A3* or *COL4A4* mutation and represents the carrier state for recessive disease [14–16].

In X-linked Alport syndrome, the pathogenic mutations are different in nearly every family and more than 2500 have been reported to date [17, 18]. Fifteen percent of these variants have arisen de novo. Forty percent are missense changes, 10% are nonsense, 40% are complicated mutations, often resulting in downstream nonsense changes, and 10% affect a splice site. In general, nonsense mutations are associated with more severe clinical features than missense variants, with an earlier age at kidney failure [19, 20] and an increased likelihood of lenticonus and fleck retinopathy. Most of the missense mutations are glycine (Gly) substitutions, since Gly is the smallest amino acid and fits easily within the triple helix. Its replacement with any other amino acid in a collagenous sequence disrupts this structure. Substitutions of Gly are nearly always pathogenic, and substitutions with a glutamic acid, aspartic acid or arginine are typically associated with more severe disease [21, 22]. These genotype-phenotype correlations mean that it is possible to use the type of mutation to predict the approximate age at kidney failure onset.

Disease-causing variants in autosomal recessive Alport syndrome are compound heterozygous changes in the *COL4A3* or *COL4A4* genes, or homozygous variants where the parents are often consanguineous [6]. Many fewer pathogenic variants have been identified in *COL4A3* or *COL4A4* than *COL4A5*, but again the same variant types indicate the likelihood of severe disease (large rearrangements, insertions, deletions, nonsense mutations, splicing variants, certain Gly substitutions) and a younger age at kidney failure onset. Thus, in autosomal recessive Alport syndrome, two nonsense mutations result in earlier onset kidney failure than one nonsense and one missense mutation, which in turn are associated with an earlier onset than two missense mutations [18, 23].

Pathogenesis

The GBM is abnormal in both X-linked and autosomal recessive Alport syndrome, with thinning, and later thickening, lamellation, subepithelial frilling, and intramembranous deposits [24, 25].

The GBM lies between the epithelial and endothelial cells of the glomerular capillary loop and comprises mainly type IV collagen, a triple helix of three of the six α chains [26]. These chains are encoded by the *COL4A1–COL4A6* genes, which are found in pairs (*COL4A1-2*, *COL4A3-4, COL4A5–6*) head-to-head on chromosomes 13, 2, and X, respectively. In infancy, the GBM collagen IV consists of mainly the α1α1α2 heterotrimer, but it is replaced at about 2 years of age with the α3α4α5 network. In adults, the α3α4α5 network is found in the basement membranes of the glomerulus, distal tubule, cochlea, lens capsule, cornea, and retina, and the collagen IV α1α1α2 network persists in the vascular membranes. The collagen IV α5α5α6 heterotrimer is found in Bowman's capsule and the dermis epithelium.

Mutations in *COL4A5* in a male result in loss of the α5 chain from the collagen IV triple helix and of the other chains that form the α3α4α5 heterotrimer. Initially the GBM is thinned but over time there is a compensatory increase in collagen IV α1α1α2. This network is more susceptible to proteolysis, which contributes to successive episodes of thinning, repair, and eventual lamellation and scarring [24, 27]. In a female with X-linked Alport syndrome, lyonization means that each cell produces either a normal collagen IV α3α4α5 heterotrimer or none in the cells where the mutation is expressed. In autosomal recessive Alport syndrome, the two *COL4A3* or *COL4A4* mutations result in the loss of both copies of the corresponding α3 or α4 chain, and subsequently the whole α3α4α5 network. There are similar changes in the other tissues affected by Alport syndrome.

Heterozygous mutations in the *COL4A3* or *COL4A4* gene result in the loss of about half the collagen IV α3α4α5 network from the GBM, producing thinning. This thinning does not change over time, in contrast to the appearance in boys, girls, and women with X-linked Alport syndrome, where lamellation develops.

The mechanisms by which mutations in the Alport genes result in disease have not been well studied in humans but are probably the same as for other collagen diseases. Thus, with missense mutations there is likely to be a build-up of misfolded protein in the endoplasmic reticulum (ER) leading to ER stress and autophagy. Nonsense mutations may result not in truncated proteins but rather in "nonsense-mediated decay" with the destruction of the corresponding mRNA [28, 29].

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Clinical features

The typical clinical features of Alport syndrome are hematuria, progressive impairment, anterior lenticonus, and a fleck retinopathy (Tables 69.1 and 69.2, and Figure 69.1) [2, 19, 20, 32, 33]. Most of these features may be present in children.

X-linked disease in males. Hematuria in boys with X-linked Alport syndrome is present from infancy. Transient episodes of macroscopic hematuria may occur with coincidental respiratory tract infections. Proteinuria develops at a variable age from childhood to adolescence or later. Kidney failure occurs as young as 7 years, with 40% of men having renal failure by 30 years and 90% by the age of 40 [17, 19, 20].

The hearing loss is first noted from about the age of 6 and is a bilateral, high-tone sensorineural defect. Speech discrimination is well-preserved but hearing aids are generally helpful.

Table 69.1 Clinical features in X-linked Alport syndrome in boys and girls, other causes, and management.

Characteristic of Alport syndrome (OMIM 301050)	Clinical features in boys and girls with X-linked Alport syndrome	Other causes	Management
Hematuria	Persistent microscopic hematuria occurs in all affected boys and girls from infancy, together with episodes of macroscopic hematuria with coincidental respiratory tract infections	Thin basement membrane nephropathy; IgA disease; atypical hemolytic uremic syndrome; post-streptococcal glomerulonephritis; causes of nonglomerular hematuria such as polycystic kidney disease	Confirm the diagnosis and mode of inheritance of Alport syndrome with genetic testing; cascade testing of other at-risk family members; provide genetic counseling to family members
Proteinuria	Persistent, from childhood or adolescence in boys and typically later onset in women	Focal and segmental glomerulosclerosis	Minimize any proteinuria with ACE inhibitors etc.; control BP adequately; provide kidney failure support
Kidney function impairment; end-stage kidney failure	Age at end-stage kidney failure is determined by underlying mutations, but also by coincidental nephrotoxic medications, hypotension, sepsis	Glomerulonephritis, nephrotoxic medications, hypotension, sepsis	Preemptive kidney transplantation; confirm that the kidney donor is not affected using genetic testing if necessary
Hearing loss	High tone sensorineural hearing loss, first noted at about the age of 6 years in boys and in middle age in women	Hearing loss also occurs with many other inherited kidney diseases, e.g. mitochondrial diseases, branchio-oto-renal syndrome, and with dialysis treatment	Be vigilant to prevent learning issues; screen all affected individuals with audiometry at presentation; provide hearing aids early to maximize hearing retention
Lenticonus	Not present until third decade in males and not present in girls or women	No other cause known Lenticonus is pathognomonic for Alport syndrome Difficulty with visual focusing; needs frequent changes to prescription glasses	Lens replacement when necessary
Fleck retinopathy	Present in more than half the boys with X-linked Alport syndrome, especially by end-stage kidney failure onset; may occur in adolescent girls but often later	No other cause known Fleck retinopathy is pathognomonic for Alport syndrome	Fleck retinopathy does not affect vision nor need treatment
Anti-GBM disease post transplant	<2% of affected boys but not affected girls	Must be differentiated from acute rejection	Difficult to predict, but appears to depend on the underlying mutation; diagnosed on transplant biopsy; cannot be detected with conventional anti GBM assays; recurs with subsequent grafts

(*Continued*)

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Table 69.1 (Continued)

Characteristic of Alport syndrome (OMIM 301050)	Clinical features in boys and girls with X-linked Alport syndrome	Other causes	Management
Additional features			
Leiomyomatosis (ATS-DL, OMIM 308940)	Rare (<1% of all patients with Alport syndrome), only occurs with contiguous gene deletion extending from *COL4A5* into *COL4A6;* a common presentation is difficulty with swallowing from late adolescence; present in all affected boys and girls with these mutations	No other cause known for familial hematuria and leiomyomatosis	The diagnosis is confirmed histologically and with genetic testing
Intellectual disability (Alport syndrome, mental retardation, midface hypoplasia, elliptocytosis) (ATS-MR, OMIM 300194)	Very rare, associated with midface hypoplasia, elliptocytosis and intellectual disability; another contiguous gene deletion; only described in boys	No other cause known for this syndrome	Diagnosis is confirmed with genetic testing
Vascular aneurysms (aortic, intracranial)	Very rare; noted incidentally or at the time of rupture; may rupture in adolescence [30]	Other causes of end-stage kidney failure and aneurysms include polycystic kidney disease, Ehlers–Danlos syndrome, Marfan syndrome [31]	Diagnosis is confirmed with genetic testing; blood pressure control is critical

Table 69.2 Clinical features in young people and adults with X-linked or autosomal recessive Alport syndrome.

	Boys and adolescent males with X-linked Alport syndrome	Adult males with X-linked Alport syndrome	Girls and women with X-linked Alport syndrome	Males and females with autosomal recessive Alport syndrome
Hematuria	From early infancy in all boys	Hematuria in all	Hematuria in 95%	In all, from early infancy
Proteinuria	Often by adolescence	Almost all	30% of women in middle age	Often by adolescence
Kidney failure	May occur in children, but average age at onset is 21 years with severe mutations	90% have end-stage kidney failure by the age of 40	20–30% have end-stage kidney failure by the age of 60	Often before 20 years of age
Hearing loss	Starts from the age of 6, present in many adolescents	50–80% have a clinical hearing loss and 85–100% on audiometry	Very common by 40 years of age	Almost all
Lenticonus	Not reported in childhood	30%	Not reported	Very common, at least 40%
Fleck retinopathy	Earliest at age 8 years, up to 60% by end of adolescence	80%	Uncommon in girls, but 70% of women	Very common, 70%

Lenticonus does not occur in children or adolescents [33]. Only men with X-linked disease and men and women with autosomal recessive Alport syndrome have lenticonus. The lens can be replaced and lenticonus does not recur after surgery. A fleck retinopathy has been reported from the age of 8, but is more common in adolescence. It does not affect vision nor require treatment. Other ocular complications are rare.

X-linked disease in females. Girls and adolescents have hematuria from childhood, some develop proteinuria as adults, and 20–30% have end-stage kidney failure by the age of 60 [13, 32]. It is unclear why some women develop kidney failure, but it is often only one woman in a family. Kidney failure in such cases may be better explained by poorly controlled hypertension, diabetes or renovascular disease than by the mutations.

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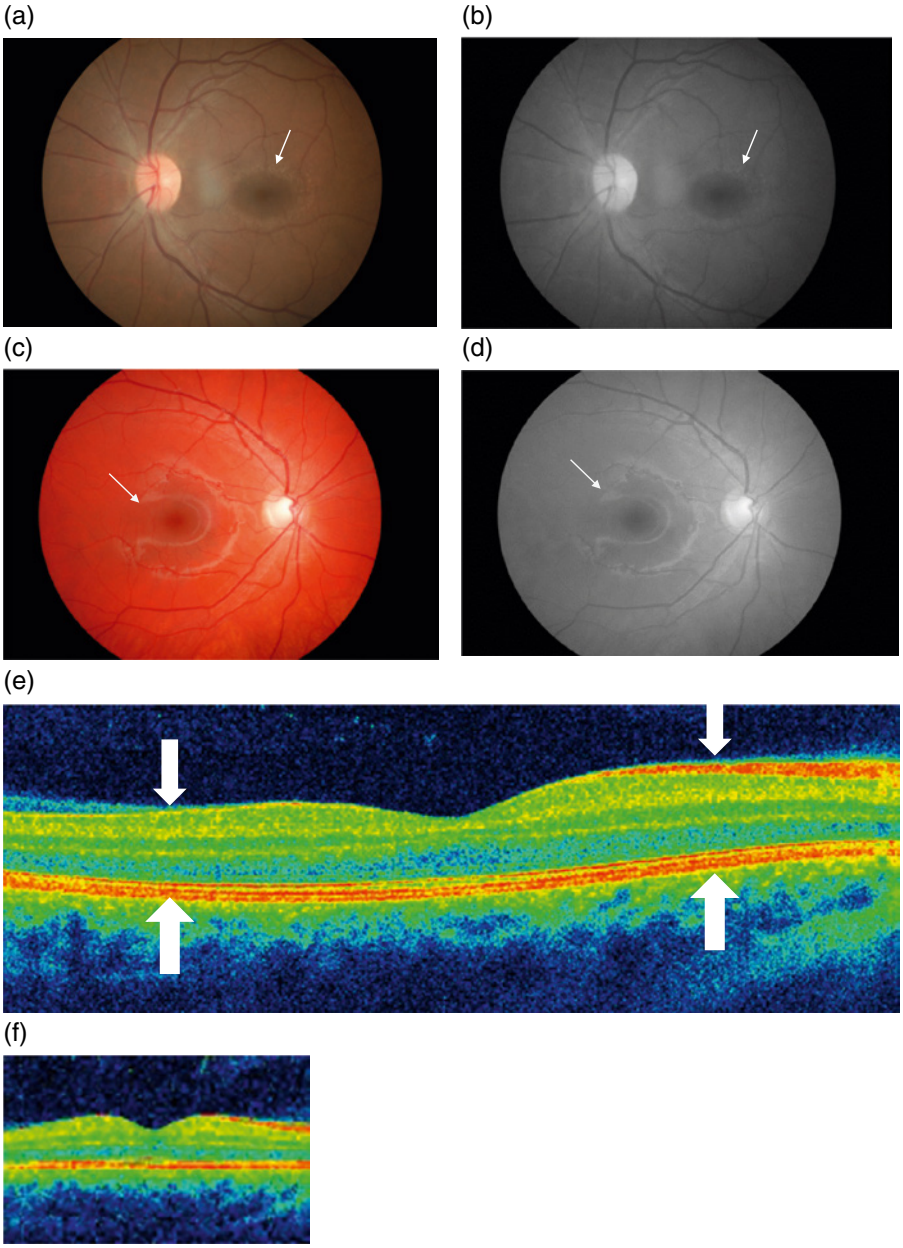

Figure 69.1 (a) Color retinal photograph of a 12-year-old boy with X-linked Alport syndrome demonstrating the typical perimacular fleck retinopathy (arrow) that spares the fovea. (b) Black and white view demonstrating more clearly the perimacular fleck retinopathy (arrow). (c) Color retinal photograph of a 14-year-old boy with thin basement membrane nephropathy demonstrating the normal retinal sheen (arrow) which is simply the light reflection seen in young people. The fleck retinopathy has to be distinguished from this normal appearance. (d) Black and white view illustrating the normal retinal sheen (arrow). (e) Optical coherence tomographic (OCT) appearance of the retina demonstrating that the temporal retinal thickness is much less than the nasal retinal thickness (arrows). (f) Normal OCT appearance where both nasal and temporal retinal thickness are similar.

Many affected middle-aged women have a hearing loss. Women with X-linked disease do not develop lenticonus, and the central fleck retinopathy is less common than in men. However, 70% have a peripheral fleck retinopathy.

Autosomal recessive Alport syndrome. Autosomal recessive Alport syndrome is much less common than X-linked disease but is often confused with this condition. The clinical features in boys and girls with autosomal recessive Alport syndrome are indistinguishable from those in boys with X-linked disease and severe mutations. Affected boys and girls with recessive disease caused by two severe mutations have hematuria from infancy and develop proteinuria, renal failure, hearing loss, and central fleck retinopathy in their teens, at an earlier age than those with only one severe mutation or none [23].

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A number of features suggest autosomal recessive inheritance [3]:

- The age at onset is often younger than for X-linked disease. Thus, children may develop end-stage kidney failure by 10 years of age with hearing loss and retinopathy.
- Disease occurs in only a single generation, sporadically or in siblings.
- Boys and girls are affected equally often and equally severely. Girls have features more typically seen in boys with X-linked disease, with renal failure, hearing loss, and retinopathy.
- The family may be consanguineous or have originated from the same relatively isolated geographic region. The family may be unaware of the consanguinity from previous generations.

Testing a boy or girl with autosomal recessive Alport syndrome for proteinuria, renal impairment, hearing loss, and fleck retinopathy is likely to yield one of these features by the age of 15 years. Both parents will have a heterozygous *COL4A3* or *COL4A4* mutation and thin membrane nephropathy, and the mother and possibly the father will have hematuria, but no proteinuria, normal renal function, and no other features of Alport syndrome.

Diagnosis of X-Linked or Autosomal Recessive Alport Syndrome

The diagnosis of Alport syndrome is suspected where the typical clinical features are present, especially if there is a family history of the disease, hematuria or kidney failure, hearing loss, lenticonus, or fleck retinopathy. The diagnosis is confirmed most accurately with genetic testing, usually with whole exome sequencing [3].

Another frequently used diagnostic method is the demonstration of a lamellated GBM on electron microscopy of a renal biopsy [3]. However, the GBM may be thinned without lamellation in a boy or girl, or their mother with X-linked disease, and there may be no distinctive features in an end-stage kidney. Some laboratories use GBM immunohistochemistry where GBM typically lacking the collagen IV α5 chain confirms the diagnosis of Alport syndrome [34], but this technique is not widely available and staining is more difficult to interpret in girls and women.

Genetic testing has the advantage of not only confirming the diagnosis but also identifying the mode of inheritance [6]. The distinction between the X-linked and autosomal recessive forms of Alport syndrome can be difficult to interpret even from a three-generation pedigree, where families are small and include only women or children, or uncharacterized relatives. However, the mode of inheritance is critical because of the implications for other family members. Thus, for a man with X-linked disease, none of his sons but all his daughters inherit the mutation. For a woman with X-linked disease, half her sons and half her daughters have the mutation, and all her affected sons develop kidney failure. This contrasts with autosomal recessive Alport syndrome, where the offspring of an affected person all have only one copy of the mutation and none develops Alport syndrome or kidney failure.

Clinicians often want further evidence suggesting Alport syndrome before proceeding with genetic testing. Examining the affected individual carefully, as well as the parents and siblings, is often very helpful.

For a boy with hematuria:

- Finding that he has proteinuria, renal impairment, hearing loss or a fleck retinopathy is consistent with X-linked or autosomal recessive Alport syndrome. The presence of proteinuria or kidney function impairment suggests X-linked Alport syndrome more than thin basement membrane nephropathy.
- Finding that he has hearing loss. This is consistent with both X-linked and autosomal recessive Alport syndrome but also with many other inherited renal diseases and coincidental middle ear infections.
- Finding that he has fleck retinopathy. This is consistent with both X-linked and autosomal recessive Alport syndrome.
- Finding that his mother has no hematuria suggests that a mutation has developed de novo or that this is not X-linked Alport syndrome or thin membrane nephropathy.
- Finding that his mother has hematuria but no other features of Alport syndrome is consistent with the boy having thin membrane nephropathy and X-linked or autosomal recessive Alport syndrome.
- Finding that his mother has proteinuria, renal impairment, hearing loss or a fleck retinopathy suggests X-linked Alport syndrome.
- Finding that his father has hematuria is consistent with the boy having thin basement membrane nephropathy or autosomal recessive Alport syndrome, but not X-linked Alport syndrome.

For a girl with hematuria:

- Hearing loss and a fleck retinopathy are not usually present if she has X-linked Alport syndrome. However, where present, proteinuria, hearing loss or fleck retinopathy suggest X-linked or autosomal recessive Alport syndrome.

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- Finding that her mother has hematuria is consistent with thin basement membrane nephropathy, or X-linked or autosomal recessive Alport syndrome. Where her mother does not have hematuria, the mutation may be inherited from her father or has arisen de novo.
- Finding that her mother has a hearing loss or fleck retinopathy increases the likelihood of X-linked Alport syndrome or of autosomal recessive Alport syndrome.
- Finding that her father has hematuria is consistent also with thin basement membrane nephropathy, X-linked or autosomal recessive Alport syndrome.

Treatment

To date, very few randomized controlled treatment trials have been undertaken in Alport syndrome. It has been necessary for international experts to collaboratively produce guidelines for the management of these conditions [3, 6, 13, 35], largely based on the following studies. While limited data is available from case series and animal models, large multicenter interventional studies addressing new agents and protocols are underway (Table 69.3).

Angiotensin Converting Enzyme Inhibitor

There is no cure for Alport syndrome, but a retrospective analysis of the European Alport Registry of 174 treated and 109 untreated individuals demonstrated that early use of angiotensin converting enzyme (ACE) inhibitors delayed end-stage renal failure in boys with X-linked disease by up to 13 years [36]. The subjects included 33 boys with hematuria or microalbuminuria, 115 with proteinuria, and 26 with renal impairment, who were followed for a mean duration more than 20 years. With treatment, no boy with hematuria or microalbuminuria developed end-stage kidney failure, but those with renal impairment developed end-stage kidney failure at a median of 25 years and those with proteinuria at a median of 40 years. This contrasted with their untreated relatives, who developed end-stage kidney failure at a median of 22 years. Commencing ACE inhibitors at an earlier age resulted in a progressive delay in the age at end-stage kidney failure onset through both reducing proteinuria and interstitial fibrosis, the latter through opposing transforming growth factor β (TGFβ) (Table 69.3). Hypertension control is less important because it often occurs late in Alport syndrome. Side effects

Table 69.3 Recommendations for the treatment of Alport syndrome.

Treatment	Recommendation	Certainty of evidence	Strength of recommendation
ACE inhibitors	We suggest the use of ACE inhibitors in X-linked Alport syndrome: in boys, starting use as soon as possible, and in girls, from the onset of proteinuria	Moderate (retrospective registry data) strongly suggests that ACE inhibition delays kidney failure and increases life expectancy in both boys and girls. This recommendation is also based on the compelling observational evidence of renoprotective effects of ACE inhibitors.	Moderate [36]
	We suggest the use of ACE inhibitors in autosomal recessive Alport syndrome: in boys and girls, as early as possible	Moderate (retrospective registry data) strongly suggests that ACE inhibition delays renal failure and increases life expectancy in both boys and girls	Moderate [36]
Angiotensin receptor blockers (ARB)	We suggest the use of ARB to reduce proteinuria in Alport syndrome	Strong evidence for reducing proteinuria	Moderate [37]
Combination of ACE inhibitors and ARB	We suggest the combination of ACE inhibition and an ARB reduces proteinuria more than a single agent in Alport syndrome (subject to satisfactory K level)	Strong evidence for reducing proteinuria more than ACE inhibitor or ARB alone; the combination is also more effective in other kidney diseases associated with proteinuria	Moderate [38]
Aldosterone blockade in addition to ACE inhibition and ARB	We suggest that the addition of aldosterone antagonist to ACE inhibitor or ACE inhibitor in combination with ARB may have a further beneficial effect in reducing proteinuria in children with Alport syndrome (subject to satisfactory K level)	Strong evidence for further reducing proteinuria compared with the combination of ACE and ARB inhibition; also effective in other renal diseases associated with proteinuria	Moderate for proteinuria, but very low for likelihood of delaying renal failure onset [39]

ACE, angiotensin converting enzyme.

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such as cough were rare, occurring in only 5% of treated individuals. This study's major limitation was that it was a registry review and not a randomized controlled trial regarding the efficacy of ACE inhibition to delay end-stage kidney failure. However, the effects of ACE inhibitors in Alport syndrome are similar to those seen in other forms of glomerulonephritis and in several studies of diabetic nephropathy and the results have recently been confirmed in a randomized control trial [40].

The results of ACE inhibitor treatment of 205 heterozygous carriers of X-linked Alport syndrome and 29 carriers of recessive Alport syndrome with thin basement membrane nephropathy were similar to those described in individuals with Alport syndrome, where renin-angiotensin-aldosterone system (RAAS) inhibition significantly delayed the onset of end-stage renal failure [41]. One hundred and eleven patients (47%) of the cohort received nephroprotective treatment at a mean age of 28 years at start of therapy. Of these, 53 (47%) had proteinuria, 27 (24%) had renal impairment, and 17 (15%) had microalbuminuria. One hundred and nine were treated with ACE inhibitors, 34 with angiotensin receptor blockers (ARBs) and 21 with both, for an average of 5.8 years (range 1–21 years). Six (5%) reached end-stage kidney failure. One hundred and twenty-four patients received no nephroprotective therapy. They had milder disease, with 20 having proteinuria (18%) and 7 (5%) renal impairment. Twenty-eight reached end-stage kidney failure (25%). Thus, the likelihood of end-stage kidney failure was less in treated patients and end-stage kidney failure occurred later in treated than untreated disease ($P < 0.0001$). Both these cohorts included children and adolescents. The authors concluded that RAAS blockade delayed the onset of end-stage renal failure in Alport carriers with proteinuria who received therapy before the onset of end-stage kidney failure. They emphasized that there was no selection bias in the treatment group, indeed the treatment group had more proteinuria and renal impairment. However, this was again a registry review with known limitations of observational studies. There were also too few carriers of autosomal recessive Alport syndrome for them to be examined separately.

In general, the ACE inhibitor, ramipril, is recommended as the agent of choice for treating children because of its safety profile [35], but a beneficial effect has been demonstrated only in small case series and in animal models.

Combination Therapy

The age at end-stage renal failure may be further delayed with the addition of ARB and aldosterone antagonists to ACE inhibitors (subject to satisfactory K levels) (Tables 69.3 and 69.2). In one study, 306 children aged 1–17 years with proteinuria completed a randomized double-blind 12-week trial of losartan versus amlodipine or placebo. Losartan treatment significantly reduced proteinuria compared with amlodipine or placebo: -35.8% (95% CI -27.6% to −43.1%) versus amlodipine/placebo 1.4% (95% CI–10.3% to 14.5%), $P \leq 0.001$. Adverse events were few and comparable in all groups. In a further subgroup analysis, the authors randomized 27 of these subjects to losartan ($n = 15$) or enalapril ($n = 12$), and their proteinuria and renal function followed. Losartan maintained the reduction in proteinuria, but enalapril produced a further reduction over the 3 years of study. There were no serious drug-related adverse effects with either agent [37]. However, this study had limitations. It was underpowered, Alport syndrome was diagnosed clinically, patients could be given further medications at their clinicians' discretion, and there was no placebo arm.

The combination of ACE inhibitor and an ARB is even more effective [38]. Ten children with proteinuria and a mean age of 12 years ± 4.1 years were randomized to treatment with an ACE inhibitor or ARB for 3 months and then combination therapy for a further 3 months. The investigators demonstrated that the combination of agents reduced proteinuria by –80.21% ± −10.75 at the end of the 6-month trial. This was a significant reduction compared with no treatment. Left ventricular hypertrophy also was reduced.

Finally, the effect of aldosterone blockade has been examined in five patients, aged 11 – 19 years of age, three with X-linked and two with so-called autosomal dominant Alport syndrome, all with a lamellated GBM and persistent proteinuria >0.2 g/g urinary protein creatinine (UPC) [39]. Treatment with an ACE inhibitor ($n = 1$) or ACE inhibitor/ARB combination ($n = 4$) and spironolactone 25 mg daily resulted in a reduction in UPC ratio to 0.13 ± 0.06 g/g at 18 months but no change in eGFR. However, one patient developed a serum $K > 5$ meq/l, and another developed renal failure.

Newer agents undergoing evaluation for the treatment of Alport syndrome include some that target the interstitial fibrosis that correlates best with renal impairment, and bardoxolone with its effects on antioxidant and anti-inflammatory activity. The aim of current treatments is to further delay renal failure rather than to effect a cure. Although there is currently no specific treatment for missense and nonsense mutations, future therapies are likely to directly target the mechanisms by which mutation types cause disease, namely ER stress and nonsense-mediated decay, respectively [42]. Correction of a genetic defect in stem cells is still too difficult and carries too much risk to be clinically useful when compared with the low risk and the efficacy of renal transplantation.

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Renal Transplantation

Children with X-linked or autosomal recessive Alport syndrome typically undergo pre-emptive renal transplantation. In X-linked disease, it is important that the donor is not an affected family member, which in most cases excludes the mother [3, 13], because her inherent risk of renal failure is amplified by the additional load on her residual kidney after donation [3].

Many renal physicians also discourage donation from the parent of a child with autosomal recessive Alport syndrome since they are themselves likely to be heterozygotes and already have an increased risk of renal impairment.

Individuals with Alport syndrome who undergo renal transplantation have a better outcome than others with end-stage kidney disease [43]. There is a very small risk of post-transplantation antiGBM disease [44], but antiGBM antibodies are directed against different epitopes from antiGBM disease and cannot be detected with routine assays [44].

Thin Basement Membrane Nephropathy

Introduction

Definition

Thin basement membrane nephropathy, previously known as benign familial hematuria or benign persistent hematuria, is characterized by hematuria, minimal proteinuria, normal blood pressure and kidney function, and a benign course [1]. The GBM is thinned without the lamellation seen in Alport syndrome [30]. Thin membrane nephropathy is caused by heterozygous mutations in the *COL4A3* or *COL4A4* genes [14, 16, 45] and represents the carrier state for autosomal recessive Alport syndrome [15, 16].

Epidemiology

Thin basement membrane nephropathy affects at least 1% of the population [9] but, like Alport syndrome, is often unrecognized.

Inheritance of thin membrane nephropathy is autosomal dominant, and boys and girls are equally likely to have a heterozygous *COL4A3* or *COL4A4* mutation. There are two peaks in the age at presentation [1]. Children first come to attention by the age of 7, when they are often detected because of infection-associated macroscopic hematuria or through screening programs on starting school.

The second peak in presentations is in young or middle-aged women whose hematuria is noted incidentally on testing for insurance or employment purposes, or at postnatal visits [1]. Interestingly, in later life men appear to be affected less often than women because they are less likely to have hematuria. This is probably because their GBM is normally thicker and the mutation-associated thinning is not sufficient to allow the transient GBM breaks through which red blood cell escape [46].

Most, but not all, children with thin membrane nephropathy also have another affected family member with hematuria [1]. A child with hematuria is more likely to have a mother with hematuria than a father. Even if a child has inherited the mutation from their father, he may not have hematuria, so the familial nature is not apparent.

Pathophysiology

The demonstration of a single heterozygous *COL4A3* or *COL4A4* pathogenic variant is consistent with thin basement membrane nephropathy being the carrier from of autosomal recessive Alport syndrome [14–16].

Relatively few mutations have been reported in thin membrane nephropathy, but the mutation types are likely to be the same as for autosomal recessive Alport syndrome, that is, 10% nonsense variants, 30% complex variants, 10% splice site changes, and 40% missense variants. Most reported missense variants are Gly substitutions, but it may simply be that Gly substitutions are easier to identify as pathogenic.

There are no data on genotype-phenotype correlations for *COL4A3* and *COL4A4* heterozygous variants in thin membrane nephropathy [47]. In particular, too few variants have been described in individuals with proteinuria, hypertension or renal impairment to determine genetic risk factors. In addition, coincidental causes, such as superimposed IgA disease [48] or additional mutations in other podocyte genes [49], are rarely sought routinely.

Glomerular podocytes produce the collagen IV α3α4α5 heterotrimer, and a mutation in the *COL4A3* or *COL4A4* gene results in about half the amount of the corresponding collagen IV α3 or α4 chain and of the α3α4α5 network, resulting in GBM thinning, transient breaks, and hematuria. It is unclear why proteinuria is not more prominent in thin membrane nephropathy when GBM gaps are observed, but one explanation is that proteinuria is normally reabsorbed by the tubules and any that persists reflects secondary FSGS. Alternatively, sometimes proteinuria or renal impairment in thin membrane nephropathy occur because of mutations in other podocyte genes [49].

Diagnosis

The diagnosis of thin basement membrane nephropathy is suspected clinically where there is persistent glomerular hematuria, but minimal proteinuria and normal blood

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pressure and renal function [1]. In many cases, especially in children, a renal biopsy is not undertaken where thin membrane nephropathy is suspected. Sometimes a mother or grandmother will have already undergone biopsy, in which case, the GBM is thinned but not lamellated, often with increased mesangial expansion and cellularity, and sometimes with secondary FSGS.

Current recommendations are that a boy or a girl with thin basement membrane nephropathy does not necessarily need to have their diagnosis confirmed with genetic testing.

However, genetic testing is warranted if X-linked or autosomal recessive Alport syndrome cannot be excluded. Thus, any child with hematuria but also proteinuria, hypertension, renal impairment, or hearing loss, or with a family history suggesting Alport syndrome or renal failure, should have genetic testing rather than a renal biopsy [6]. Genetic testing not only confirms the diagnosis of thin basement membrane nephropathy, but also of X-linked or autosomal recessive Alport syndrome.

Where a child with hematuria is identified, both the parents and any at-risk family members should be screened for hematuria and reviewed for the clinical features of Alport syndrome. Risk factors that indicate genetic testing is warranted include a family history of Alport syndrome or renal impairment, proteinuria, a lamellated GBM in a family member, hearing loss, lenticonus, or fleck retinopathy.

These recommendations may mean that some children, especially girls with X-linked Alport syndrome, will be misdiagnosed with thin membrane nephropathy. This occurs especially where the family comprises only females or young boys, or where late-onset Alport syndrome occurs.

Where a child is demonstrated to have thin membrane nephropathy, other family members are also likely to be affected. One of the child's parents usually has the mutation but not necessarily hematuria. In general, half the siblings of a child with thin basement membrane nephropathy will also have the mutation and half the child's future offspring have the mutation too.

Prognosis

Complications from thin basement membrane nephropathy are rare in early life but children should be reviewed at least annually to ensure they do not develop complications of thin membrane nephropathy or features of Alport syndrome. The child's affected parent will also need to be reviewed regularly by their family doctor.

The prognosis of thin membrane nephropathy for children is excellent. However it remains difficult to differentiate clinically thin membrane nephropathy from X-linked Alport syndrome in girls and in boys with mutations associated with mild or late-onset disease.

There is a biased reporting of individuals with thin basement membrane nephropathy from hospital clinics rather than from primary care practitioners, which means that that they are more likely to have complications such as proteinuria and impaired kidney function. It remains unclear how often thin membrane nephropathy-associated mutations are associated with proteinuria and end-stage kidney failure.

Treatment

In general, thin membrane nephropathy does not require treatment. However, proteinuria and hypertension are best treated with ACE inhibitors and, if necessary, ARBs and aldosterone antagonists.

Conclusions

Thin basement membrane nephropathy is the commonest cause of inherited kidney disease, but usually has a benign course. Its genetic basis is known but the risk factors for proteinuria and renal impairment are still not completely understood.

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Shigatoxin-related Hemolytic-uremic Syndrome

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Introduction

Hemolytic-uremic syndrome (HUS) is a common cause of acute kidney injury and an important etiology of acquired chronic kidney disease (CKD) in children [2]. Traditionally, childhood HUS was classified as typical or diarrhea-associated (D+HUS) and atypical (aHUS) or diarrhea-negative (D-HUS). More recently, classification within the larger family of thrombotic microangiopathies has been based on etiology and pathophysiology: infectious, genetic/hereditary, autoimmune, or metabolic [3]. In children, 90% of HUS cases are preceded by infections with Shiga toxin-producing *Escherichia coli* (STEC-HUS) heralded by a prodrome of diarrhea [4]. Most children with STEC infections suffer only from a self-limited severe infectious enterocolitis associated with hematochezia but 10–15% progress to develop HUS with potentially devastating acute and chronic complications [5]. Despite increasing understanding of the pathophysiology and highly effective drugs recently made available for other forms of HUS, management of STEC-HUS continues to be based mostly on supportive measures [6].

This chapter examines the evidence for management of STEC infections to STEC-HUS continuum.

Definition

HUS is defined as a fast drop in hematocrit to ≤30%, platelet count to $\leq 150 \times 10^3/\mu l$, and a rise in serum creatinine concentration to above the upper limit of normal for age [5]. Schistocytes on blood smear are characteristic of the underlying thrombotic microangiopathy (TMA) but are not pathognomonic of HUS. Diagnosis of STEC-HUS is confirmed by detection of STEC strains or Shigatoxin (STX) in stool samples but may be presumed if HUS was preceded by an enterocolitis with diarrhea and hematochezia or based on epidemiological confirmation of an infection source causing an outbreak.

Epidemiology

HUS is a rare disease with an incidence ranging from 0.7 to 8 cases/100 000 population per year with significant geographical and seasonal variability. The highest incidence of D+HUS is reported among children younger than 6 years who typically present in the late summer and autumn months [7]. Prevalence of STEC-HUS is closely related to the incidence of STEC infections and the main reservoir for such pathogens is the gastrointestinal tract of healthy cattle [8, 9]. Higher incidence of STEC-HUS has been reported in rural areas at northern latitudes with a developed cattle industry [10]. The highest incidence of STEC-HUS in the world was reported in Argentina, while in Canada it has been observed in the province of Alberta; in both geographic regions beef production is a major component of local agriculture and economy [7, 11–13]. Large outbreaks originating in contaminated food have been extensively publicized; one of the best-known outbreaks in the United States was caused by contaminated ground beef hamburgers served in a fast-food restaurant chain, hence the popular name for STEC-HUS: "hamburger disease" [14–16]. However, contrary to popular belief, most cases of STEC-HUS are sporadic or occur in small clusters and are not related to poorly cooked contaminated ground beef. The majority of sporadic cases, as well as small and large outbreaks, are caused by other contaminated foods and beverages, such as vegetables, cider, or milk, and transmission from person to person has also been reported [17, 18]. Moreover, not all outbreaks of STEC-HUS are associated with STEC infections; other pathogens may be responsible, the most common of which is Shigella dysenteriae type 1 (SD1) [19].

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Pathophysiology

Gasser et al. were the first to describe the triad of symptoms and coin the term "hemolytic-uremic syndrome" in 1955, but only in 1983 were Karmali et al. able to identify the toxin produced by STEC as a causative factor [20, 21]. Notwithstanding Karmali et al.'s important discovery, HUS was reported to be associated with SD1 infectious diarrhea as early as 1975 [22]. The toxin isolated from stools of patients with STEC infections causing HUS was first named "verotoxin" due to its extremely toxic effect on Vero cells, an epithelial cell line isolated from the kidneys of African green monkey [21, 23]. Subsequently, two toxins were identified and reclassified as "Shiga-like toxins" (STX1 and STX2) due to their close similarity to the Shiga toxin produced by SD1 [24]. The Shiga toxins are produced by pathogens in the gut and are absorbed into the blood circulation, which delivers them to various organs, including the kidneys. Progression from STEC infection to STEC-HUS has been documented to be associated almost exclusively with pathogens sectoring STX2 alone or in combination with STX1 [25]. In fact, co-expression of STX1 in the presence of STX2, has recently been showed to be protective [26].

Shiga toxins are composed of five β-subunits that bind with high affinity to the globotriaosylceramide receptor (Gb3) and an α-subunit, which, after being internalized by cells, interferes with the ribosomal apparatus, effectively blocking protein synthesis and leading to cell death [27]. The currently accepted mechanism leading to HUS is a TMA triggered by endothelial cell death, exposure of the subendothelial space, and activation of the thrombotic cascade. Extensive microangiopathic intravascular thrombosis is responsible for hemolysis of red cells by fragmentation, platelet consumption, and decreased glomerular perfusion leading to kidney injury. However, in addition to a prothrombotic effect, the presence of STX in microvasculature has been shown to be vasoconstrictive, proadhesive, and proinflammatory. Recent scientific evidence suggests that the extent of endothelial cell injury observed in STX-related HUS exceeds expectations from interference with protein synthesis alone [27]. in vitro experiments demonstrated that bacterial lipopolysaccharide (endotoxin) acts synergistically with SD1 and STEC toxins to enhance endothelial damage and the coagulative microangiopathy. [28] One of the additional emerging mechanisms for cell injury in STX-related HUS involves activation of the complement system. In fact, evidence demonstrating activation of the complement system in STEC-HUS forms the basis for the hypothesis on the existence of a common pathogenetic mechanism unifying all forms of TMA, including aHUS and thrombotic thrombocytopenic purpura (TTP) [29].

In North America and Europe, *E. coli* O157:H7 producing both forms of STX is the most common serotype isolated from stools of STEC-HUS patients, but many other serotypes have been reported to trigger STEC-HUS: O11:H8, Ol03-H2, O123, O26, and more [30]. The mega-outbreak that occurred in Germany in 2011 was caused by *E. coli* 0104:H4, which was previously not known to cause outbreaks on such a scale [27, 31].

Diagnosis

Early effective supportive intervention depends on a high level of suspicion of STEC infection in all children presenting with acute enterocolitis associated with hematochezia followed by diligent close monitoring for emerging HUS diagnostic markers. Failure to obtain a stool sample at presentation may seriously impact the likelihood of STEC isolation or STX detection [32]. Culture of stool samples requires time and special conditions, and has limited rates of success, but new methods of screening stool samples for STX by enzyme-linked immunosorbent assay and polymerase chain reaction have greatly improved the likelihood and speed of detection [33]. More recently, multiplex molecular panels for diagnosis of gastrointestinal infections, based on protein-to-creatinine ratio (PCR) technology, promise to allow accurate point-of-care detection of STX and producing pathogens [34].

Diagnosis of evolving HUS requires sequential blood testing for monitoring hematological and biochemical markers of TMA and ultimately HUS: hematocrit/hemoglobin, platelet count, and serum creatinine. Increasing serum lactate dehydrogenase (LDH) and declining haptoglobin levels can further confirm hemolysis while detection of schistocytes on blood smear highly supports mechanical red cell damage such as occurs in TMA/HUS.

Prognosis

Infectious STEC enterocolitis as well as evolving TMA underlying STEC-HUS are self-limited; a majority of patients with STEC-HUS, including children with very severe acute disease courses, experience full recovery based on clinical and laboratory assessments [5, 6, 35]. Nevertheless, a significant percentage are affected by long-term, mostly renal, sequelae, and mortality rates continue to be reported at 2–4% [36–38]. Prior to availability of acute RRT, mortality rates in children reached more than 30%. Unlike mortality rates, risk for long-term renal sequelae has not significantly changed over the years, remaining around 30%, with 3–5% of children affected by STEC-HUS developing stage 5

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CKD [37, 39]. Children with identifiable sequelae such as hypertension, proteinuria, or impaired renal function should be treated according to best practices for nonspecific CKD management. Most such patients are likely to benefit from long-term nephrology follow-up. However, children that seem to have made a full recovery may also benefit from long-term monitoring, as the extent of nephron loss during the acute phase cannot be accurately assessed [39].

While the kidneys are always affected by STEC-HUS, the acute phase may be complicated by extrarenal pathology, the most serious of which involves the central nervous system (CNS) and accounts for most observed mortality. Seizure, coma, and stroke are among the most frequent CNS complications, which overall affect up to 25% of STEC-HUS patients [40]. The gastrointestinal tract is also frequently affected by STEC-HUS beyond injury caused by the prodromal enterocolitis. Bowel or intestinal perforation and stricture, pancreatitis with evolving diabetes mellitus, as well as injury to all other components of the gastrointestinal system have been reported [41]. Involvement of other systems such as respiratory, musculoskeletal, and cardiovascular are rare, but have been documented [41].

Treatment

Antibiotic Treatment

Antibiotic treatment of STEC infections before and after development of D+HUS has been a subject of great interest for researchers (Table 70.1). However, most available data were obtained from retrospective and some prospective cohort studies demonstrating conflicting results [42–50]. Prospective, blinded, and randomized studies have not been conducted, and observational studies have been affected by bias toward use of antibiotics in initially "sicker" patients. A number of meta-analyses and systematic reviews have attempted to summarize the results of available studies, reaching inconclusive results and stating that more prospective, appropriately powered studies are needed [51–53]. However, a more recent meta-analysis that excluded reports with high risk for bias concluded that use of antibiotics for treatment of STEC infections was associated with an increased risk of developing HUS [54]. Most studies found no difference or favored a negative

Table 70.1 Treatment for STEC HUS.

Treatment	Recommendation	Certainty of evidence	Strength of recommendation
Antimicrobial therapy	We suggest avoiding antimicrobial treatment of STEC infections or STEC related HUS with antimicrobials due to the reported association with increased risk for worse outcomes	Moderate to low (a number of meta – analyses and systematic reviews demonstrate a negative effect of antibiotics on outcomes)	Weak as the evidence is contradictory and randomized prospective studies are missing
Erythropoietin	We suggest that erythropoietin may be considered for treatment of STEC-HUS related hemolytic anemia to minimize exposure to red blood cell transfusions	Very low	Weak as the evidence is based on a very small sample size
Intravenous fluid volume expansion	We suggest that volume expansion with an isotonic intravenous fluid solution in children with STEC infection or STEC-HUS, having adequate urine output with no to mild fluid overload, may be associated with better outcomes	Low (a meta-analysis based on observational data, prospective randomized studies are lacking)	Weak
Renal replacement therapy	We suggest avoiding delays in initiation of RRT for treatment of STEC-HUS related AKI, according to universally accepted indications and using the safest and most readily available modality	Low no studies available except descriptive reports	Weak
Terminal complement inhibitors	We suggest that the use of terminal complement inhibitors in STEC-HUS is not routinely indicated but it should be considered in patients suspected of atypical HUS	Very low (Case reports and series with contradicting conclusions)	Weak

GRADE assessment of the certainty of the evidence [1]: High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different* is low. Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different* is moderate. Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different* is high. Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different* is very high. **Substantially different = a large enough difference that it might affect decision-making.*

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impact of antibiotics on risk for STEC-HUS and outcome [51, 52]. Only one retrospective cohort analysis of a large outbreak that occurred in Japan demonstrated benefit for using the antibiotic fosfomycin within the first 2–3 days from beginning of STEC infection symptoms. Among 130 children aged 6–11 years, the odds ratio (OR) for developing HUS was less than 1.0 if fosfomycin was given within 3 days from start of infection symptoms compared to no antibiotics [44]. The reduction in odds ratio was statistically significant when the antibiotic was started even earlier, within the first 2 days of illness (adjusted OR 0.09, 95% confidence interval [CI] 0.01–0.79) [44]. The negative impact of antibiotic use on risk and outcomes of HUS is not well understood. in vitro exposure of bacteria to antibiotics induces lysis with release of toxin, which, in the gut, could potentially be more likely to be absorbed [55, 56]. However, a toxin binder designed to diminish toxin absorption was not proven effective in a prospective randomized controlled trial [57]. Antibiotics have not been shown to directly influence interaction between toxins and their Gb3 receptor, suggesting that the antibiotic influence on risk and outcome of HUS is mediated by modulation of toxin bioavailability [58–60]. Recently, further evidence for a possibly beneficial role of early use of antibiotics in patients with D+HUS was provided by the retrospective analysis of antibiotic use during the 2011 German mega-outbreak [31]. Nevertheless, based on best available evidence, the current recommendations are to avoid use of antibiotics in treatment of STEC infections [54].

Shiga Toxin Binding and Blocking Agents

STX1 and STX2 are highly potent toxins in very small concentrations. Blocking STX access into the bloodstream or inactivation of blood-borne STX are major areas of interest in the search for D+HUS treatment options. SYNSORB Pk (Synsorb Biotech Inc., Calgary, AB, Canada) is a synthetic potent STX binder that was designed to bind STX in the gut, thus blocking absorption of STX; unfortunately, a large phase III trial with this agent failed to demonstrate any benefit [57].

Blocking the effect of blood-borne STX with inactivating antibodies has also been attempted, but currently the results of a trial with monoclonal anti-STX1 and anti-STX2 antibodies have not been reported [6, 61]. The main challenge with STX binding and blocking agents has been timing of administration, which needs to occur before the STX effect is further amplified by a cascade of events involving the thrombotic, inflammatory, and complement systems [6, 57].

Fluid Management in D+HUS

The benefits of early intravenous fluid expansion for management of STEC infections are supported by a growing body of evidence. Retrospective analysis by Oakes et al., Balestracci et al., Ojeda et al. and others have shown that dehydration at presentation is associated with increased risk for HUS complications such as oligoanuria, need for renal replacement therapy (RRT), neurological complications, and death [62–64]. On the contrary, early proactive intravenous fluid expansion with isotonic solutions was shown in retrospective and prospective studies by Ake et al., Hickey et al., and Ardissino et al. to reduce risk for HUS complications [65–67]. A meta-analysis that pooled these data demonstrated that dehydration at presentation with HUS was associated with increased risk for oligoanuria (OR 2.38, 95% CI 1.30–4.35), RRT (OR 1.90, 95% CI 1.25–2.90), and death (OR 5.13, 95% CI 1.50–17.57), while intravenous fluid administration up to the day of HUS diagnosis was associated with a decreased risk of RRT (OR 0.26, 95% CI 0.11–0.60) [68]. However, once STEC-HUS develops and oligoanuria is identified, careful fluid management, including restriction, should be considered to avoid fluid overload. Fluid overload that is present at the time of initiation of urgent RRT in critically ill children with multisystem involvement has been shown to be a bad prognostic factor [69, 70]. Among other benefits, close monitoring during the STEC infection is important to facilitate early detection of evolving HUS and allow timely necessary adjustments to fluid management. As HUS and acute kidney injury evolve, hypertension frequently develops along with fluid and salt retention. In this situation, general principles for management of acute kidney injury in children should be applied [71, 72]. Careful attention should be given to the type of fluids administered, aiming to minimize salt load, while total administered volume should not exceed the total of all losses such as urine output, insensible losses, ongoing diarrhea, etc. The volume required for adequate nutrition should be given priority and be included in the total fluid balance. Judicious use of loop diuretics can help manage hypertension as well as maintain adequate urine output, which can facilitate fluid management and nutrition, and improve outcomes [73]. Additional use of antihypertensive agents may be needed to control hypertension.

Renal Replacement Therapy

RRT is required in 50–70% of cases in the acute phase of HUS [7, 37]. There are no specific indications or benefit for early initiation of acute dialysis in D+HUS [6]. General indications for acute RRT in the management of

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acute kidney injury should be applied. Oligoanuria, severe azotemia, electrolyte abnormalities, acidosis, and need for nutritional support are among the common indications for acute dialysis [74]. There is no clear benefit for a specific type of RRT, but peritoneal dialysis has been extensively and successfully used in children with D+HUS [75, 76]. Insertion of a peritoneal dialysis catheter can usually be safely performed in thrombocytopenic patients without the need for platelet transfusion, and trained staff can safely perform peritoneal dialysis on general pediatric wards [6, 76, 77]. Complications and technical failure are rare despite the severe intestinal injury caused by the STEC infection, which is not a contraindication for peritoneal dialysis and does not interfere with the effectiveness of this modality [75]. Hemodialysis or continuous veno-venous hemodiafiltration are also very efficient, but require appropriate venous access and admission to an intensive care unit. Nevertheless, in patients with aHUS or in whom aHUS is suspected, hemodialysis or veno-venous hemodiafiltration may be preferred modalities since the venous access can also be used for administration of plasma exchange, which is generally indicated in these patients. Finally, despite the fact that there is no proven benefit for early RRT, efforts should be made to start dialysis before development of fluid overload, which may be associated with a worse prognosis in a critically ill child [70, 78].

Erythropoietin and Transfusions

Platelet consumption and hemolysis are integral consequences of the TMA in HUS. Thrombocytopenia in these cases can be extreme, yet platelet transfusions are not indicated unless there is evidence of active bleeding. Transfused platelets may enhance the thrombotic events occurring in various microvasculature beds of affected patients [79]. Severe anemia secondary to hemolysis, on the other hand, can further destabilize patients by negative effects on the cardiovascular and respiratory systems. Erythrocyte transfusions are considered an important component of the supportive therapy in HUS, and have been reported to be required in up to 92.6% of patients [80]. Use of erythropoietin (EPO) early in the course of HUS has been proposed as a possible measure toward reducing the need for erythrocyte transfusions [81]. A small prospective study that randomized 10 children with HUS to early EPO vs. placebo found that EPO significantly reduced the required number of red blood cell (RBC) transfusions (0.2 vs. 1.4, $P < 0.04$, *t*-test) [81]. However, a more recent retrospective study did not support these results, therefore further studies are needed to evaluate the routine use of EPO in patients with STEC-HUS [82].

Complement Inhibitors

Currently, the single commercially available complement inhibitor is eculizumab, a recombinant, humanized monoclonal antibody against complement component C5. This antibody effectively blocks cleavage of complement factor C5 and the formation of the complement membrane attack complex C5b-9 [83]. Clinical trials and postmarketing prospective observational studies have demonstrated that eculizumab is very effective and superior to plasma therapy for prevention and treatment of aHUS episodes caused by dysregulations of the complement system [84]. A role for eculizumab in management of STEC-HUS is not established. [85] However, in view of evidence demonstrating complement activation associated with STEC infection and HUS, exploratory use of eculizumab in patients with STEC-HUS has been attempted. A letter to the editor published in the *New England Journal of Medicine* in 2011 described prompt recovery after administration of eculizumab in three children with severe STEC-HUS, associated with RRT and severe CNS complications [86]. However, in the same year, widespread use of eculizumab during the mega outbreak of HUS in Germany led to a high-quality retrospective review which did not demonstrate an outcome benefit for 67 out of 298 patients who were treated with this agent, compared to matched patients who did not receive eculizumab [31].

A recent narrative review published in 2018 included 11 reports and reached the conclusion that current evidence cannot support or disprove a role for eculizumab in the management of STEC-HUS and a clinical trial is desperately needed [87].

Conclusions

Most cases of childhood HUS evolve as a devastating complication of an infectious STEC colitis in otherwise healthy children. There is currently no specific treatment for STEC colitis or HUS that is supported by high-quality evidence, but timely and appropriate supportive care has been associated with good outcomes in the majority of patients. Low-quality evidence supports some measures that appear to be associated with better outcomes: intravenous volume expansion in children with STEC colitis at risk for or with imminent HUS and avoidance of antibiotics for treatment of the STEC colitis or HUS. Erythropoietin may limit the number of blood transfusions and early intervention with RRT may lower the risk associated with fluid overload, but the evidence for these interventions is of very low quality. Routine use of terminal complement inhibitors such as eculizumab is not supported by currently available

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evidence, but in view of physiological plausibility and positive case reports further investigation in this matter is justified. Moreover, there is currently no evidence supporting an intervention that may decrease the risk of progression from STEC-infectious colitis to HUS. However, preliminary indications that early intravenous volume expansion with isotonic fluids may be effective should be investigated in a randomized prospective trial.

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Part 12

Patient-centered Care and Outcomes

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71

Shared Decision-making

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Introduction

The chronic kidney disease (CKD) journey, from diagnosis to end-of-life care, includes many complicated treatment decisions that require patients and physicians to consider the risks and potential benefits of life-extending treatments and therapies. The impact of treatment decisions on a patient's life vary significantly from minor changes in their daily routine (e.g. having to begin daily medication to control blood pressure or limiting salt intake in their diet) to life-altering changes that accompany life-prolonging therapies (such as thrice weekly hemodialysis).

The trade-off made between the burdens and benefits of any given treatment will differ for each patient depending on their values and preferences. Many patients rely on their clinicians for guidance on treatment decisions that are not only in their best prognostic interests, but also align with their values and preferences. Over the last few decades, the clinician's role in treatment decision-making has shifted from paternalism to partnership, and it is now recognized that clinicians should engage in shared decision-making (SDM) to determine the most appropriate course of treatment for each patient.

Nephrology clinicians frequently face situations such as in the example in Box 71.1 in which they inform and guide patients to make treatment decisions about their kidney disease and how to manage accompanying setbacks. In addition to dialysis modalities and transplantation, comprehensive conservative care (CCC) is an elected treatment path that emphasizes quality of life and symptom management. For older patients, especially those with advanced conditions, dialysis may not offer meaningful longevity or quality of life [1–5]. Patients managed without dialysis are more likely to have their symptoms alleviated, spend survived time out of the hospital, and receive dedicated end-of-life care with services such as hospice [6, 7]. Yet, patients are less likely to understand these prognostic trajectories or the options available to have treatment without dialysis and choose CCC [8].

SDM in nephrology care is an essential component to ensuring patients make informed decisions that reflect their priorities. In SDM, clinicians and patients work together to make decisions that balance the potential risks and expected benefits with patient preferences and values. This chapter provides a summary of the evidence for SDM in nephrology care, particularly for older patients with advanced comorbidities facing difficult decisions about treatment of advanced kidney disease and preferences for end-of-life care. The chapter includes a definition of SDM, communication strategies to facilitate clinicians in engaging in SDM, and patient decision aids aimed to prepare patients to consider their values and preferences with the treatment decision.

Definition

SDM has been defined as the meeting of two experts – the patient and clinician – with the goal of working together to make the best healthcare decision for the patient. The concept of SDM is countered by traditional models, including paternalistic and informed models [9] (Figure 71.1). Within the paternalistic model, the clinician is viewed as the expert

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Box 71.1 Case Example

Ms. K is a 75-year-old wheelchair-bound woman with progressive stage 4 kidney disease due to heart failure and diabetes who is seen in nephrology clinic for management of advanced kidney disease. She requires assistance for bathing and dressing, and recently moved into a personal care home. The nephrology clinician has cared for Ms. K over 3 years and notes a progressive decline in function and health. Reflecting on the treatment decisions that she and Ms. K will address, the clinician asks herself:

- How do I help Ms. K make the right decision to manage her advanced kidney disease?
- How do I prepare Ms. K to make the right decisions to manage her future end-of-life care?

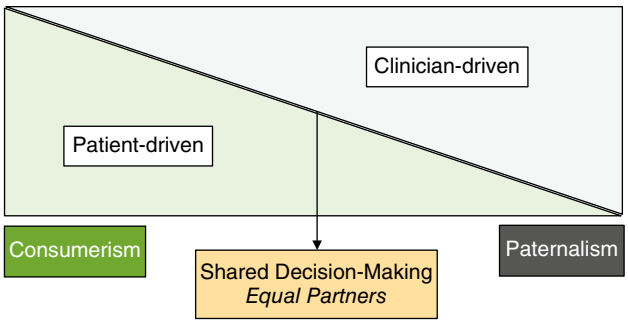

Figure 71.1 Continuum of patient–clinician decision-making models.

and so uses their skills to determine the best treatments based on the patient's medical condition and circumstances. The paternalistic model assumes that the clinician knows what is in the patient's best interest and hence the flow of information and deliberation is unidirectional with minimal input from the patient. A major limitation of this model is the assumption that the clinician and patient espouse similar values and views of what qualifies as benefit.

The countering model on the other end of the decision-making spectrum is the informative model. Sometimes referred to as the consumer model, the informative model shifts the role of decision-making to the patient. Within this model, the clinician provides the necessary information about the disease process, possible treatments, and expected risks and benefits with the expectation that the patient decides what is best [9]. This model lacks essential elements of the clinician–patient relationship, including helping patients to deliberate and recommending treatment decisions based on their values and preferences.

SDM responds to the limitations of these traditional models and addresses real-world challenges to decision-making within healthcare. In the case in Box 71.1, the right choice for how Ms. K manages her kidney disease and future end of life is not straightforward and depends on her individual values and priorities.

Charles and authors define SDM as requiring four necessary elements to address these preference-sensitive decisions in which no best answer exists [10]:

1) First, at a minimum, the treatment decision-making process must involve the clinician and patient.
2) Second, the process is bidirectional, meaning both the clinician and patient share information with each other.
3) Third, both the clinician and patient actively participate in the decision-making process by sharing treatment preferences.
4) Fourth, the final treatment decision is made and agreed on by both the clinician and the patient.

Shared Decision-making in Nephrology

Frameworks and Processes

The Renal Physicians Association (RPA) and the Choosing Wisely Campaign recommend nephrology clinicians engage in SDM to address complex treatment decisions such as dialysis initiation versus CCC and preferences for end-of-life care [11, 12]. Yet patients describe insufficient preparation and involvement in treatment decisions. In one qualitative study of US dialysis patients over the age of 65, no patient felt they made the choice to initiate dialysis [13]. Rather these decisions were either influenced by the perception of imminent death without dialysis or by the clinician. Among 197 dialysis patients in Canada with an average age of 53 years, 48% reported that treatment decisions were made by their clinician, with only 25% reporting shared responsibility [14].

A fundamental component of SDM in advanced kidney disease involves providing patient-specific prognostic information. Patients report rare prognosis discussions which influence how decisions for end-of-life care are made. In an interview study, incident hemodialysis patients who reported an overly optimistic prognosis were more likely to elect life-prolonging treatments if they were seriously ill, even if this meant suffering or discomfort [15]. Although there are emerging efforts to develop and validate various risk predictions models into usable forms for clinicians, such as online calculators or calculators integrated within the electronic health record, these most often focus on mortality risk and do not provide individualized information about other outcomes important to patients [16]. This omission of relevant prognostic information may in part explain why dialysis

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patients are more likely to receive intensive therapies at end of life and less likely to receive quality end-of-life care such as hospice services [7, 17].

Another component of the SDM process is for the patient and clinician together to understand the patient's values and priorities (Tables 71.1–71.5) [18]. In a survey study conducted in Australia and Canada, hemodialysis patients and their caregivers prioritized important outcomes in hemodialysis patients. They defined survival in terms of living well, with mortality ranking only 14th in terms of importance [19]. These findings reinforce that clinician focus on treatment decision-making discussions must address more than just survival alone [20].

Table 71.1 Priorities identified as important to patients with advanced kidney disease [18].

Maintain independence	Physical appearance
Flexibility in daily schedule	Social relationships (family and friends)
Privacy	Burden on others
Comfort of environment	Safety related to treatments
Reliability of treatment timing and schedule	Work or school

Source: Based on Dahlerus et al. [18].

SHARE Approach to Shared Decision-making

Multiple SDM models exist. All models reinforce the importance of prognostic information and the elicitation of patient values and priorities to guide treatment decisions [10, 21–23].

The SHARE Approach is a five-step process for SDM endorsed by the Agency of Healthcare Research and Quality [23]. The steps are (i) seek the patient's participation, (ii) help the patient explore and compare treatment options, (iii) assess the patient's values and preferences, (iv) reach a decision with the patient, and (v) evaluate the patient's decision. These steps are best accomplished through patient-centered communication strategies. The communication framework Ask-Tell-Ask supports a two-way conversation in which the clinician elicits information

Table 71.2 Characteristics of included studies.

Study ID	*n*	Study design	Setting	Participants	Topic
Dahlerus et al. [18]	180	Semistructured interviews	United States	18 years or older, eGFR <25 ml/min/1.73 m^3 or on dialysis for >3 months	Perspectives on modality choice
Davison et al. [51]	24	Ethnographic study with interviews	Canada	Purposive sample: 44–88 years (mean 64), 50% women, $n = 1$ first nations Aboriginal, $n = 23$ white	Perspectives of salient features of effective facilitated advance care planning
Fortnum et al. [44]	NA	Development of decision aid	Australia and New Zealand	NA	Shared decision-making: dialysis vs. conservative care
Harwood et al. [60]	410	Qualitative synthesis	Six databases	>18 years with chronic kidney disease	Dialysis modality decision-making
Holley et al. [61]	614	Observational survey: two time points	United States	Nephrologists	Changing clinician attitudes and practices of end-of-life decision-making
Hussain et al. [49]	270	Qualitative synthesis	Four databases	Patients aged 26–93 years, health professionals aged 26–61 years	Factors affecting patient or health professional decisions to commence or withdraw from dialysis
Joly et al. [3]	146	Cohort study	France	Consecutive pre-ESRD octogenarians referred to nephrology unit	Factors affecting clinician and patient choice of dialysis or conservative care in octogenarians, and impact on survival
Moattari et al. [62]	48	Randomized controlled trial	Iran	Patients on hemodialysis	Effect of empowerment on self-efficacy and quality of life (including decision-making)
Morton et al. [54]	462	Qualitative synthesis	Six databases	Patients with chronic kidney disease and caregivers	Decision-making and choice for dialysis, transplantation or palliative care

eGFR, estimated glomerular filtration rate; NA, not applicable.

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Table 71.3 Impact on patient-centered care and outcomes.

Study ID	Impact on patient-centered care and outcomes
Dahlerus et al. [18]	More informed/engaged patients who were active in decision-making chose options that better fit their priorities. Important outcomes that impact decision-making were quality of life, convenience of at home therapy, ability to work, risk of infection, and medical expertise.
Davison et al. [51]	Most patients believed healthcare providers wanted to know their preferences for advance care planning and believed this would influence outcomes of treatment. Patients based their decisions on the impact of the care plan on their personal lives and wanted to know how interventions could help achieve personal goals, e.g. avoiding hospitalization.
Holley et al. [61]	Significantly more nephrologists in 2005 were willing to stop dialysis in a severely demented patient (53% vs. 32%, $P<0.00001$) and to withhold dialysis from a permanently unconscious patient (90% vs. 83%, $P<0.001$). Most nephrologists in both surveys would respect the request of a competent patient to stop dialysis. When asked whom they would consult to assist in decision-making for each of these hypothetical cases, <98% would consult the patient's family in each scenario in both 1990 and 2005. In 2005, compared with 1990, nephrologists are more likely to honor a dialysis patient's wish for DNR status.
Hussain et al. [49]	For many patients the effects of treatment on their quality of life was more important than medical effectiveness – quality of life was prioritized over longevity/survival. As life on dialysis deteriorated, patients questioned its worth and considered withdrawal. Knowing they had this option gave them control. Health professionals depended on biomedical criteria to guide decision-making rather than patient preference, delaying withdrawal until medically necessary.
Joly et al. [3]	Aside from patient refusal, late referral, social isolation, low functional capacity, and diabetes may have oriented the medical decision to withhold dialysis.
Moattari et al. [62]	A significant change was observed between the groups in terms of stress reduction (adjusted mean difference −3.6 [−4.4 to −1.57], $P<0.02$) as well as the decision-making dimension (adjusted mean difference −3.21 [−4.39 to −2.03], $P<0.001$) and overall self-efficacy scores (adjusted mean difference −12.02 [−18.41 to −5.53], $P<0.001$). Also, a significant difference was found in the overall mean score of quality of life and in all dimensions of the quality of life between the groups (adjusted mean difference −2.93 [−4.39 to −1.47], $P<0.001$).
Morton et al. [54]	Medical outcomes of treatment were considered less important than the effect of treatment on patient's lifestyle. Longevity was viewed as less important than quality of life.

Table 71.4 Communication.

Study ID	Prognosis, preferences
Davison et al. [51]	Patients wanted more information earlier in the disease process – this promoted self-reliance, alleviated fear/uncertainties, helped prepare them for future, and gave them the knowledge to make decisions that were compatible with their values and beliefs. Patients wanted clear honest discussions in lay language. They explained that jargon caused confusion and misunderstanding. They believed physicians were responsible for initiating discussions around end-of-life care.
Hussain et al. [49]	More information about their future was considered better than none by patients, despite fears/uncertainty this may raise. It was important to patients that information was delivered by a trusted person.
Morton et al. [54]	Framing of treatment/interventions by physicians impacted patient decisions, e.g. Transplant framed as a 6-h operation with risk of death was seen as not worth it by some patients, despite increased rate of survival.

from the patient (Ask) before giving relevant information (Tell) and then assesses how the information impacted the patient's understanding (Ask).

Seek the patient's participation (Step 1): The first step of the SHARE Approach is to invite the patient's participation in SDM. This can involve establishing rapport, reinforcing patient's autonomy, and the patient's preferences for decision-making. Both clinician and patient are expected to collaborate proactively in this decision-making process by exchanging information about the illness, diagnosis, and treatment from their areas of expertise, outlining explicit values and preferences in the context of care pathways and/or lifestyle, reasoning together to determine the best option for the patient, and agreeing and implementing the choice that aligns best with clinical evidence and patient preference. Establishing rapport and trust is an important aspect of seeking patient participation. This involves gaining an understanding of the patient's experience and culture

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Table 71.5 Barriers to SDM.

Study ID	Barriers to SDM
Dahlerus et al. [18]	Medical crisis/need was prioritized over patient choice. Physician control over decision limited patient involvement in decision-making.
Davison et al. [51]	Patients less likely to actively engage in decision-making process if they did not perceive any benefit (e.g. aligned priorities). The use of medical jargon was confusing for patients and discouraged them from participating in decision-making. A lack of family support also prevented patients from participating in shared decision-making.
Hussain et al. [49]	The perceived power and dominance of the healthcare team hindered patient involvement in medical decision-making. The healthcare team were considered to "own" the knowledge and they decided what the patient should know. Lack of time for acutely unwell patients meant decisions were made without including them. Inconsistent and "accidental" delivery of information left patients unable to participate in shared decision-making as they did not understand their treatment options and the respective consequences of each.
Morton et al. [54]	Lack of information about all available treatment options limited patients' involvement in their treatment decisions. Physiological contraindications (e.g. no vascular access) eliminated treatment options in the eyes of physicians in favor of biomedical outcomes. Limited healthcare resources (e.g. availability of chair/kidneys) meant patients' options were also limited. Problematic timing of presenting information to patients by physicians meant they were sometimes too sick or did not have enough time to absorb information.

which may involve traditions, beliefs, and values based on cultural norms [24, 25]. In addition, seeking participation also involves determining the patient's desired level of involvement in the decision-making process. Some patients may prefer a passive role, deferring decision-making to a loved one, or may elect a clinician-centered approach that is more directive [26]. This preference to limit their involvement or defer the final decision to the clinician can be respected and the SHARE Approach can be adapted to support these decision-making preferences and needs.

The first *Ask* of the *Ask-Tell-Ask* framework starts with gaining the patient and/or family's input rather than reflectively disclosing information. Open-ended questions such as "What have the doctors told you about your kidney disease?" allow the clinician to explore what the patient understands about their condition. These exploratory questions also allow the clinician to learn decision-making preferences, cultural experience, and belief system (Box 71.2).

Box 71.2 Seek Patient's Participation (Step 1)

The clinician caring for Ms. K wants to learn about her experience with her disease and learn how much involvement Ms. K wants in her treatment decisions and who, if any, are the other people that will be involved in the decision-making process. To determine these important aspects, the clinician asks Ms. K:

- Can you tell me about the impact your treatment has had on your life so far?
- As your clinician, what would be helpful for me to know about you and your life?
- How much involvement have you had in other medical decisions? Has this worked for you? Why/why not? Do you want to do this differently?
- Who would we include in these discussions and decisions?

Help the patient explore and compare treatment options (Step 2): This step involves detailed explanations and discussions of the potential treatment options available to the patient, including the expected benefits and risks associated with each one. This step addresses the *Tell* of the *Ask-Tell*-Ask framework. This *Tell* should include information about treatment options, including prognostic information, and should be given in a way that is clear without medical jargon.

Discussions about prognosis are often avoided until forced, either in the setting of decline or after prompted by the patient. This may be due to the inherent uncertainties regarding prognosis. While prognostic tools exist to help predict how a patient might respond to a given treatment, significant uncertainty remains for how a patient will actually do [27–29]. This uncertainty challenges the clinician's skills in guiding treatment decision-making and helping prepare patients for living with a life-prolonging treatment. Yet, many patients do want information about what to expect in the future, and prefer that this information be given voluntarily by the clinician [30].

Understanding what prognostic information the patient desires can influence the kinds of information the clinician should provide [31]. Prognostic information should include both survival and quality of life to ensure the patient receives information that addresses their personal concerns. During discussions of treatment options, it is helpful

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to describe the different treatment paths in terms of the expected benefits or potential risks ("Choosing to start dialysis may extend your life, but it may also mean that you spend more time in hospital and depend on others for help") (Box 71.3).

Assess the patient's values and preferences (Step 3): After sharing prognostic information and relevant treatment options, the conversation should shift from giving information (*Tell*) toward eliciting goals and values (*Ask*). This process ensures the decision is guided by what matters most to the patient, such as quality of life, level of independence, and preferences for care at the end of life. This also may be integrated throughout the therapeutic relationship between patient and clinician over time. In a small study of 99 dialysis patients reflecting on their recent experience with selecting a treatment option for advanced kidney disease, 20% reported that their doctor asked about their values and preferences [8]. In a recent study of 271 patients with stage 4 or 5 nondialysis-dependent CKD from one center, patients most commonly identified maintaining independence as their top priority (49%). However, when the clinician was asked about the top priority of the patient only 31% (95% CI 26% to 37%) were in agreement [20]. There continues to be significant opportunity to increase the activities in clinical care in support of eliciting and understanding values and preferences.

Learning what matters most to patients involves learning patient goals and values. These "big picture" goals and values are best elicited with open-ended questions that explore hopes for, as well as worries about, the future [32–34]. By asking about hopes for the future, the patient can consider the values and priorities that are most important and whether these values and priorities support a treatment focused on quantity or quality of life. In addition to understanding what the patient hopes for in the future, it is as important to explore what the patient hopes to avoid. These concerns may be related to physical suffering, psychological distress, and being a burden to loved ones. Asking the patient about their worries provides insight into the conditions or health states that a patient hopes to avoid. For patients whose goals are focused on comfort, worries may include going back to the hospital, being away from the family or living in dependent condition (Box 71.4).

Reach a decision with the patient (Step 4): The fourth step involves offering a treatment recommendation that incorporates the prognostic data and the patient goals. For patients with older age and advanced comorbidities, the relevant treatment options are trial of dialysis (hemodialysis or peritoneal dialysis) versus CCC. Many patients desire a recommendation from the clinician while a minority of patients do not. Therefore, it is helpful to *ask permission* to provide a recommendation. If the patient agrees, the clinician can proceed with a recommendation that is grounded in the patient's own goals and values (Box 71.5).

Evaluate the patient's decision (Step 5): After the treatment path is elected, the SDM process continues and includes opportunities to reassess and revisit the care plan. First, it is difficult to prepare a patient for exactly what to expect living with dialysis or CCC. Words often fall short compared to the lived experience. Second, uncertainty makes it difficult to adequately prepare patients for what to expect even with prognostic guidance. Third, many patients may choose dialysis as a better alternative compared to

Box 71.3 Help Explore and Compare Treatment Options (Step 2)

Ms. K's nephrology clinician considers the relevant treatment options available and tailors the prognostic information based on Ms. K's clinical condition to include both survival and quality of life:

Option 1 Trial of dialysis: "For patients who are older with other advanced conditions, dialysis may add little additional time and survived time will likely include setbacks such as loss of function and more hospitalizations."

Option 2 CCC: "For patients similar to you, choosing conservative care may lead to shorter time, but time lived is focused on managing your symptoms and quality of life, without life prolonging treatments such as dialysis."

Box 71.4 Assess the Patient's Values and Preferences (Step 3)

After giving Ms. K all the relevant treatment information it is now time to elicit her priorities for treatment:

- Given this news, what is most important to you?
- As you think about the future, what concerns you the most?
- What do you want to avoid in the future?

It may be helpful to give an example comparing the two treatment options with specific potential consequences:

"Some people want to live as long as possible and choose dialysis even at the risk of frequent hospitalizations and less independence. Other people wish to focus on the quality of their lives and prefer treatments that are focused on their symptoms without dialysis even if this meant life could be shorter. Do you have a sense of how you feel about this?"

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death. Therefore patients, especially those who elect dialysis, benefit from evaluation of the decision and anticipatory guidance for future end of life needs [35] (Box 71.6). A recent study noted that it is equally important not to continually question a decision once it has been made, as this may be perceived as badgering and threaten the trust previously developed in the clinician–patient relationship [36]. Determining the intervals of re-evaluation of the treatment decision should be a part of the collaborative plan.

Evaluating the decision also involves preparation for future setbacks and end of life. Advance care planning (ACP) is a continuous process through which providers engage in discussions with patients and their families to learn their goals and preferences toward future medical treatments [37]. ACP conversations allow patients to reflect on their care preferences to inform decision-making in future declining health states. Patients who had have an ACP are more likely to receive care that is consistent with their care goals, including end-of-life care such as hospice [38]. Dialysis patients are less likely to have engaged in ACP conversations. Thus, end of life is often experienced in the hospital following life-sustaining treatments with less opportunity for quality hospice care [7]. In US nursing home patients with dementia on dialysis, those who engaged in early ACP by completing an advance directive and naming a surrogate decision-maker had fewer hospitalizations, less intensive care, and fewer invasive procedures compared to those who lacked both [39].

The SHARE Approach is generally supported by efforts to increase clinician communication skills and self-efficacy in the provision of SDM. Educational materials in kidney disease can be used in Step 2 when delivering information about treatment options, however decision tools specific to the SDM process that aim to deliver prognosis information aligned with values (Step 3) are helpful to reach a collaborative treatment decision (Step 4).

Box 71.5 Reach a Decision (Step 4)

The nephrology clinician asks Ms. K's permission prior to offering a suggested treatment plan based on what she has shared with you:

From our discussion I have a sense of what things are most important to you. Would it be ok if I offer my suggestion about a plan moving forward?

Ms. K agrees, and the clinician offers a recommendation that is supported by Ms. K's goals and priorities:

"Based on your goals to spend as much time with your family and away from the hospital even if this means shorter time, I would recommend *we pursue conservative care with a focus on your quality of life and we will not do dialysis as this would not achieve your goals. How does that sound to you?"*

Box 71.6 Evaluate the Decision (Step 5)

Patients who elect trial of dialysis especially benefit from evaluation of the decision to assess whether the treatment is meeting the patient's goals without causing unwanted burdens:

- It's been two months since we started dialysis, what has been your experience?
- When we started dialysis, we hoped that it would help you get stronger and back home. Have you been able to accomplish this goal?
- What concerns do you have with continuing dialysis?

Decision Tools

Decision aids are informational documents that present educational and prognostic information about the health condition. Information then is presented about the treatment options, and when available information about outcomes including side effects (Figure 71.2). Decision aids do not make recommendations about a specific treatment and they do not replace evaluation and counseling from a clinician. Optimized decision aids have the capability to customize the information presented to the patient using the decision aid. The International Patient Decision Aid Standards (IPDAS) Collaboration has developed criteria to assess the quality of patient decision aids using a checklist with 28 different criteria [41].

Although there has been a growing interest in the development and provision of decision aids in nephrology, few have been tested in trials to determine their impact on outcomes. The most common outcomes influenced by decision aids include addressing decisional uncertainty, knowledge and understanding, and congruence between the decision and patient values [42]. A recent review of decision aids for renal replacement therapy described 10 decision aids and another four that were more specific to conservative care [43]. Most decision aids had yet to be rigorously tested for efficacy on either decisional or clinical outcomes. The reports available support that the various decision aids are generally accepted by patients (Table 71.6). One small study examined the online self-directed decision aid http://Chooosingdialysis.org, which provides information about all treatment options but focuses on dialysis modality decisions (in-center hemodialysis or peritoneal dialysis). It was tested in 63 people (average age 59 years) and demonstrated increased kidney knowledge and less

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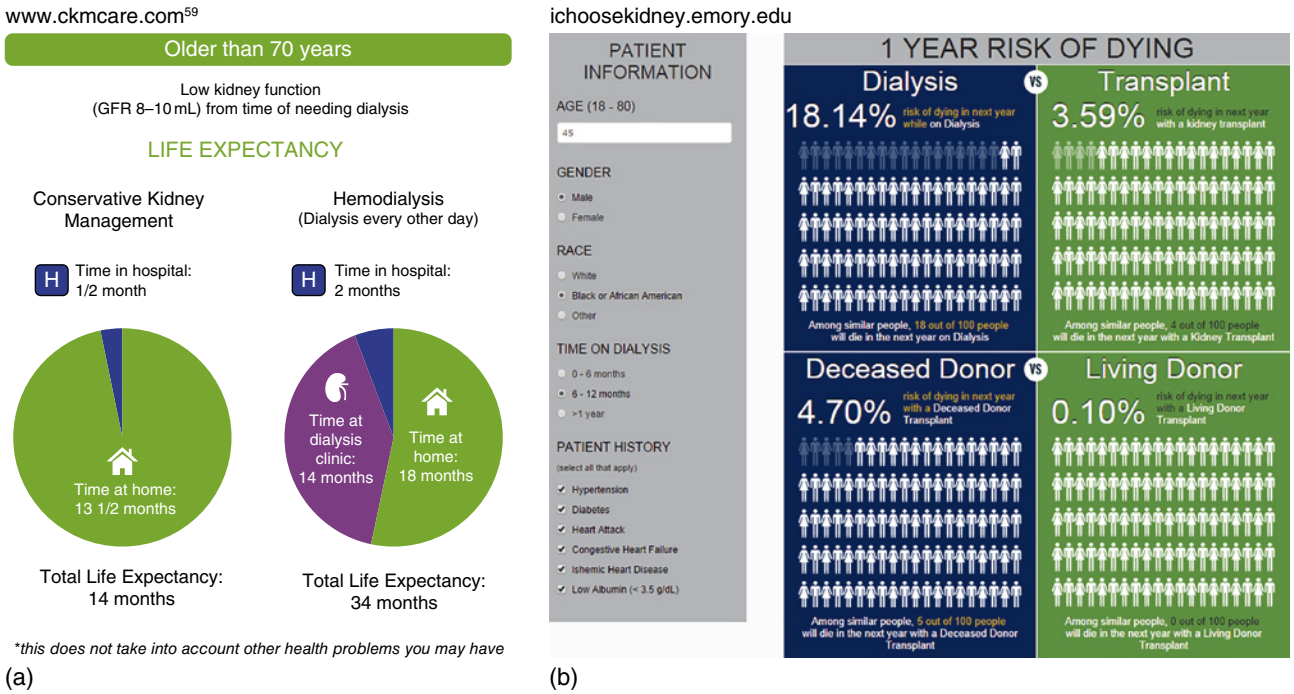

Figure 71.2 Examples of kidney decision aid content: (a) www.ckmcare.com [40] and (b) http://ichoosekidney.emory.edu.

decisional conflict after its use [48]. There was no change in decisional self-efficacy score. The largest studies reported are in the context of increasing the use of kidney transplantation as a therapy option and have shown variable results. None of the studies describe the process of using a decision aid during the clinical encounter compared to self-directed use. There are substantial gaps in knowledge regarding the use of decision aids to facilitate SDM in kidney disease care and importantly critical gaps in understanding their influence on decisional, behavioral, and health outcomes in diverse patient populations.

Barriers and Opportunities

A review of the evidence reveals potential barriers to SDM, many of which can be attributed to poor communication strategies, highlighting opportunities to address these barriers in future.

Perceived power imbalance with emphasis on lack of information: A systematic review of qualitative studies found that patients believed that the healthcare team were considered to "own" the knowledge and it was up to them to decide what patients should know [49]. A study that included interviews of 35 nephrologists from nine US states found that they generally attributed failed discussions to factors related to the patient rather than self-reflection of their own skills [50]. Participants in an interview study identified the use of medical jargon by health professionals as confusing [51]. This perception may be amplified when the patient has low health literacy which is associated with lower perceived knowledge ($r_s = 0.19$, $P < 0.0001$) among patients with advanced CKD [52] and patients with higher perceived knowledge express greater satisfaction with their clinician's communication (adjusted odds ratio 2.13 [1.59, 2.86], $P < 0.0001$). Training to improve clinicians' communication skills may directly address these potential barriers, and this may become a priority as nephrologist communication metrics have been incorporated into value-based payment systems in the United States [53].

Patients identified a lack of information about all available treatment options as a barrier to actively participating in their treatment decisions [54]. Delivery of information was labeled as "inconsistent" and "accidental," leaving patients feeling that they did not have all the information they needed to participate in SDM [49]. Complete and systematic delivery of information, using effective communication strategies, early in the diagnosis may help to address these issues. A recommended communication strategy to ensure that Step 2 is effective and that patients understand the content of the information is to perform a teach-back whereby as an example the clinician asks the patient to share how they would explain the concept or skills to their family member. This method has effectively improved self-care in kidney disease hypothesized to be due to better patient knowledge, self-efficacy, and practical skills [55].

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Table 71.6 Nephrology decision aids in support of SDM with peer-reviewed evidence.

Study ID	Description of decision aid	Summary of decisional outcomes
Kidney Supportive Care Research Group	Title: Conservative Kidney Management: Is Dialysis Right for Me Format: Web-based, printing capabilities Topic focus: Comparing dialysis options and conservative care Values clarification exercise: Yes Availability: Free; http://www.ckmcare.com/Resources/details/PDA	Not available
Fortnum et al. 2015 [44]	Title: My Kidneys, My Choice Format: Online Topic focus: Comparing dialysis options and conservative care Values clarification exercise: Yes Availability: https://mydialysischoice.org	$n = 97$ Pre-post design Increase in perceived kidney knowledge Increase in worry
Boulware et al. 2018 [45]	Title: PREPARED Format: Brochure, video Topic focus: Comparing dialysis, transplant and conservative care using checklists Values clarification exercise: No Availability: http://ckddecisions.org/prepared-materials	$n = 30$ decision aid, $n = 31$ usual care, $n = 31$ DA ± financial assistance No change in transplant preparation behaviors at 6 months 68% reported they there considering which pros and cons were more important to them
Kapell Brown et al. 2018 [46]	Title: CPR-VDA Format: Video and cardiopulmonary resuscitation decision worksheet Topic: Code status considerations in end-stage kidney disease Values clarification exercise: Yes Availability: http://vimeo.com/48147363	$n = 49$ patients, $n = 8$ family Pre-post design Knowledge score increase ($P \leq 0.0001$) Decisional self-efficacy increase ($P = 0.005$) 72% expressed no decisional uncertainty
Subramanian et al. 2018 Arbor Research	Title: http://Choosingdialysis.org: empowering patients for choices on renal replacement therapy Format: Web-based, printing capabilities Topic focus: Peritoneal dialysis, in-center hemodialysis; brief information/links other options Values clarification exercise: Yes Availability: free; http://choosingdialysis.org	$n = 63$ DA, $n = 70$ control Decisional conflict score: DA group: pre 44.3 (16.0), post 29.1 (13.7), $P < 0.0001$ Kidney knowledge: DA 90.3 (11.9), control 765 (15.3), I < 0.0001 No difference decisional self-efficacy
Patzer et al. 2017 [47]	Title: iChoose Kidney Format: Online, printing capabilities Topic: Mortality risk related to dialysis and transplant, incorporating patient variables Values clarification exercise: No Availability: http://ichoosekidney.emory.edu	Randomized trial $n = 226$ DA, I = 216 control Knowledge improvement greater in DA than in control (1.1 + 2.0 vs. 0.4 + 1.8, $P \leq 0.0001$) Transplant access similar (74.3% vs. 70.5%)

Medical crisis: In some cases patients believed that there was no time or opportunity to engage in SDM when there is a need for urgent treatment or because of a physiological contraindication (e.g. no vascular access) [18, 49, 54]. While urgent treatment decisions may be necessary in a small proportion of patients, for most there is time to present the treatment options to the patient and determine their preferences before proceeding. Also identified as a barrier was the timing of when the information was presented – some explained that it was left too late and they were too unwell or did not have enough time to absorb the information in order to make a decision [54]. The SHARE approach is

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flexible to patient needs and desire for engagement, and it allows opportunities to process the informational content while performing Step 4 to collaboratively reach a treatment decision.

A transitional care unit (TCU) program is a novel healthcare system delivery approach to address the concern regarding those who have advanced to end-stage kidney disease, who have not yet developed a treatment decisional plan, but now their medical status precludes them from fully participating in SDM [56]. This program emphasizes stabilization of medical status paired with a comprehensive educational curriculum that purposefully employed SDM techniques and decision aids. While the programs efficacy is yet to be evaluated it demonstrates that with leadership buy-in SDM can be core to the mission of integrated kidney care.

Lack of treatment options: Clinicians may perceive dialysis to be the only relevant treatment option and may therefore guide the discussion with dialysis as a default decision. In a study of Veterans Administration clinician documentation from the electronic health record, clinicians were more likely to push dialysis even when patients strongly verbalized a wish to forego dialysis [57]. Three themes that emerged described (i) dialysis as a norm in which clinicians felt obligated to repeat or reexamine the patient's decision to forego dialysis, (ii) when clinicians decided dialysis was not a viable option, this decision was justified based on biomedical factors rather than patient goals and values, and (iii) when it was determined dialysis would not be pursued, clinicians felt they had little to offer patients beyond dialysis and so often signed off from their care. Increasing education and comfort in providing CCC are strategies to overcome this "all or nothing" view of dialysis [58].

Other barriers identified were no perceived benefit of participating in SDM, lack of time during typical clinical visits, a lack of family support, and limited healthcare resources (e.g. availability of dialysis chairs) [51, 54]. Opportunities for SDM are emerging within the context of kidney transplantation organ allocation. One study found that 63% of patients wished to participate in decisions about quality of the organ [59]. This may become even more relevant as other biomarkers, including genetic information, are used for estimating risks related to graft survival.

Conclusions

SDM is a patient-centered approach to ensure patient values and priorities inform treatment decisions. SDM is especially relevant for treatment decisions for advanced kidney disease as well as end-of-life care. The SHARE Approach provides a framework for supporting SDM that ensures treatment decisions reflect relevant prognostic information and what is most important to the patient. Decision tools can help patients consider the treatment options in terms of their values and priorities. Barriers to SDM can be overcome through two-way communication, avoidance of medical jargon, and providing patients with the necessary decision tools to guide the process.

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Fatigue

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Introduction

Among patients with chronic kidney disease (CKD), fatigue is associated with cardiovascular disease and depressive symptoms [1]. Patients experience a limitation in freedom, a loss of sense of self, and social isolation [2–4]. In hemodialysis, fatigue has been identified by patients, caregivers, and health professionals as the most important patient-reported outcome to report in trials [5, 6]. In this population, it has also been marked as a predictor for cardiovascular events and mortality, independent of potential confounding risk factors such as age, diabetes, body mass index, and history of cardiovascular disease [1, 7–9]. Despite the high prevalence and importance of this symptom, fatigue remains under-recognized and undertreated.

The prevalence of fatigue in early stages of CKD (CKD stages 1–2) is unclear. This may be because CKD is often asymptomatic in earlier stages [10–12]. In CKD stages 3–5, including those on kidney replacement therapy, 54–97% of patients report fatigue [1, 13, 14]. Fatigue can be a debilitating symptom that causes emotional and physical interference in patients' lives [1, 4, 7, 10]. For patients on dialysis, 60–97% of adult patients on hemodialysis report fatigue [8] and 55–89% on peritoneal dialysis report fatigue, with increasing prevalence of fatigue over time [4, 15, 16]. Although less is known about the prevalence of fatigue in kidney transplantation, kidney recipients continue to experience severe and disabling fatigue compared to the general population [17, 18].

Although the exact cause of fatigue is unknown, it is likely to be multifactorial and different combinations of factors may contribute to fatigue as CKD progresses. Physiological factors such as anemia, uremia, comorbidities, and inflammation have shown to be correlated with fatigue [1, 11, 19, 20]. Psychosocial factors such as mood disorders and social support are also associated with fatigue [1, 11, 19, 20]. Sleep quality (including sleep apnea) may also contribute to fatigue [1, 8, 21]. It is unclear how these factors affect the frequency and severity of fatigue, but the these are potentially modifiable aspects of a patient's care that may help improve the management of fatigue.

Most of the research on fatigue in CKD has been in the hemodialysis population [21] as patients on hemodialysis experience a high symptom burden, and the fatigue experienced in this population is believed to be unique and particularly debilitating due to the nature of their treatment. However, despite the increasing number of studies of interventions to manage fatigue in the hemodialysis population, the evidence remains uncertain. The current evidence is also limited by the plethora of measures being used to assess fatigue with measures that have not been well-validated. There is also a need for more research examining onset and associated factors of fatigue in the early stages of CKD and kidney transplantation as it may contribute to identifying treatment to reduce its prevalence and severity. This chapter examines the available evidence for associated factors and interventions for fatigue across the spectrum of CKD.

Definition

Fatigue is the subjective perception of extreme and persistent tiredness, weakness, and lack of energy [22]. Traditionally,

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frameworks have conceptualized fatigue as having a dual nature: central vs. peripheral, brain vs. muscle, mental vs. physical [8, 23]. Central or mental fatigue is expressed by the inability to initiate and/or sustain concentration, motivation, and alertness. It prevents patients from participating in activities that require these functions of the brain. Peripheral or physical fatigue refers to the inability to exert or sustain muscle force. Fatigue has also been conceptualized as being on a spectrum of exhaustion and tiredness on one end, and energy and vitality on the opposite end [24]. Increasingly, multidimensional frameworks of fatigue encompassing affective, cognitive, and physical aspects are being accepted as the most suitable paradigm [10, 25]. Aspects of this complex symptom and the framework that are relevant in clinical practice and research are dictated by patient priorities and clinical importance.

Fatigue, as experienced by patients on hemodialysis, can be largely divided into two types: postdialysis fatigue and general fatigue. Postdialysis fatigue is defined as the overwhelming sense of being "washed out" immediately after dialysis [26]. General fatigue is a persistent and relentless feeling of tiredness, weakness, and lacking energy [27].

Assessment

There is a wide range of measures used to assess fatigue in patients across the spectrum of CKD. They vary considerably in terms of characteristics such as recall period, content, length, cost, and the population for which they were designed. Validation data to support the appropriateness and psychometric robustness of these measures in CKD are sparse. For example, 43 different measures were used to assess fatigue in hemodialysis without comprehensive validation data, 17 (40%) of which were developed primarily for a different patient population [28]. Validation of measures in the population of interest is necessary to ensure the accurate assessment of the outcome as psychometric properties such as content validity, reliability, and responsiveness are not always transferrable beyond the population for which it was designed and tested [29, 30].

The vitality subscale embedded in the 36-Item Short Form Health Survey (SF-36) is widely used as a measure of fatigue in CKD and other chronic health conditions [8]. While it is frequently used because it is a short, four-item scale assessing fatigue relating to the lack of energy and vitality, it is not a specific measure of fatigue. It has been criticized as a measure of fatigue because it does not capture the multidimensional nature of this symptom such as lack of motivation and weakness [8]. Vitality is also conceptualized as a different construct to fatigue, which would suggest that this measure may not adequately capture the complete patient experience of fatigue [11]. The vitality subscale has not been validated in CKD as a standalone fatigue measure. For the purposes of assessing one aspect of fatigue, the Visual Analogue Scale (VAS) may be useful for a quick assessment as it consists of one question that is easy to complete. However, explicit instructions to disaggregate sleepiness and fatigue may be needed as previous failure to differentiate between the two symptoms has been documented [21]. For a more comprehensive assessment of fatigue, the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) [31, 32] may be considered. This 13-item questionnaire demonstrated stronger associations with important clinical outcomes such as serum albumin and creatinine in patients on hemodialysis [33], compared with other measures of fatigue such as Fatigue Severity Scale and vitality subscale. However, FACIT-F is yet to be validated in the CKD population. The Chalder Fatigue Scale (CFS) has been examined in patients on hemodialysis, demonstrating good internal consistency, construct validity, and reasonable discriminant validity [33].

For assessment of postdialysis fatigue, ecological momentary assessment has been suggested as a potential method that may be able to capture the fluctuations related to dialysis more accurately while avoiding recall bias associated with patient-reported outcome measures [8, 34]. Using ecological momentary assessment to assess postdialysis fatigue involves the patients' real-time documentation of their symptom before and after dialysis. With appropriate and valid questions to assess the level of fatigue, ecological momentary assessment may be a useful tool in monitoring and improving aspects of fatigue that are treatment specific. Furthermore, a single question about the time taken to recover from a dialysis session has been used as another approach to assess the severity of postdialysis fatigue. It has demonstrated strong correlations with fatigue and vitality (SF-36 subscale), and sensitivity to change [35].

Pathophysiology

Although the exact cause of fatigue in CKD and ESRD is unknown, it is likely to be multifactorial as many variables have been suggested to contribute to the severity and prevalence of this symptom (Figure 72.1). As the disease progresses, contributors of fatigue may change. While the cause–effect relationship is unclear, various psychosocial, physiological, and treatment-related factors as well as individual characteristics have demonstrated significant

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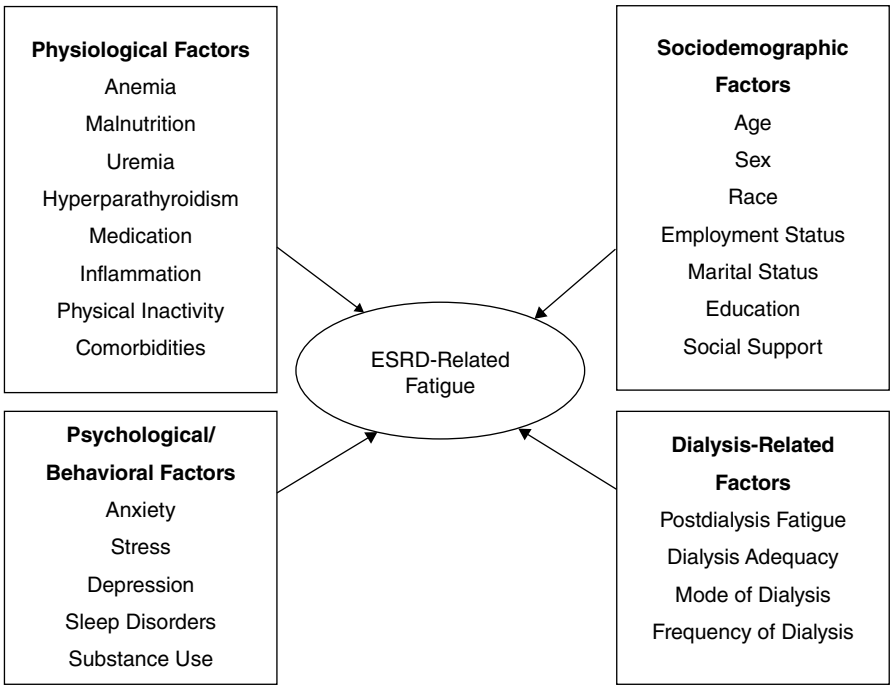

Figure 72.1 Factors affecting fatigue. *Source:* From Jhamb et al. [8].

associations with fatigue. However, these relationships are not always consistent across the literature, which limits the state of current knowledge regarding factors contributing to fatigue.

Physiological contributors have long been examined in patients on hemodialysis but a range of variables have been linked to fatigue only in the last couple of decades. Anemia is frequently cited as a speculated cause of fatigue across all stages of CKD [11] as increased levels of fatigue can be experienced as anemia develops [36]. The reduced erythropoietin (EPO) production is believed to be culpable [11]. Comorbidities such as hypertension, diabetes, heart failure, cancer, and conditions causing frailty may exacerbate fatigue [14, 20, 37]. As patients progress to CKD stage 5 and beyond, the elevated levels of inflammatory cytokines such as interleukin-6 (IL-6) may also contribute to fatigue [1, 19, 21, 38]. Such association can be seen in other chronic conditions such as multiple sclerosis, cancer, and chronic fatigue syndrome, where cytokines have been identified as contributors and even mediators of fatigue [39–42]. Some studies have found lower levels of creatinine demonstrate an association with increase in fatigue [19, 33, 43]. In advanced stages of CKD, uremia may also contribute to fatigue as it causes energy, protein, and creatinine deficiency. Dialysis adequacy is thought to have a significant role in causing uremic symptoms, including fatigue [1, 20]. Nutrient loss during hemodialysis has led to the hypothesis that malnutrition as marked by serum albumin is associated with fatigue, but more research is warranted to strengthen the inconsistent evidence [16, 19]. Fluid shifts that occur after hemodialysis are believed to cause postdialysis fatigue [11]. Furthermore, large interdialytic weight gain for patients on hemodialysis has also shown a significant relationship with lack of energy, a comparable construct to physical fatigue [44, 45].

Psychosocial factors associated with fatigue have not been well-studied in CKD. Symptoms of depression such as tiredness, lack of energy, and motivation are closely related to fatigue [46]. Thus, unsurprisingly, Depression has shown significant associations with severity of fatigue, as well as physical and mental fatigue [1, 19, 20]. Scores of fatigue were significantly higher for those who were depressed compared to those who were not. In patients on hemodialysis, postdialysis fatigue is also highly associated with depression [26]. Although it is not extensively documented in patients with CKD and end-stage renal disease (ESRD), coping mechanisms and perception of one's condition are believed to help the severity of fatigue experienced [47, 48]. Similarly, there is evidence for the role of social support as a buffer for fatigue in patients with rheumatoid arthritis [49], but this is yet to be studied in the CKD and ESRD population. However, since social support has been documented to alleviate symptoms of depression for patients on hemodialysis, it may also have a similar effect on fatigue [50].

Sleep disorders, poor sleep quality, and sleep-related breathing disorders are common in CKD and ESRD, especially in the hemodialysis population [51]. Sleep problems

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may be one of the contributors of fatigue as intuitively it is plausible to hypothesize that a lack of good sleep may result in daytime sleepiness. Sleep problems may contribute to fatigue also by increasing the release of cytokines [1] as this increase has been associated with sleep disturbances and fatigue in the general population [52]. In patients on hemodialysis, sleep disorders have been shown to be associated with reduced vitality [11, 25].

Postdialysis fatigue is a type of fatigue unique to hemodialysis patients [26, 53]. It is a fatigue associated, temporally, with the dialysis therapy session itself, and can vary in duration from minutes to several hours in length. Cross-sectional studies suggest that almost 50% of patients maintained on hemodialysis experience postdialysis fatigue lasting more than a few hours, with almost a quarter experiencing fatigue until shortly before their next treatment. Contributing factors include depression, excessive or rapid ultrafiltration, rapid and dramatic changes in osmolar, and electrolyte levels as well as possibly myocardial ischemia or stunning [53, 54].

Treatment

Due to the lack of clarity in determining the causes of fatigue, an effective treatment for this debilitating symptom also remains uncertain and difficult. Although the past decade has seen a growing number of trials assessing interventions for fatigue, evidence remains sparse and uncertain. This uncertainty can be attributed to the wide range of measures used to assess fatigue across different trials, small sample sizes, and lack of consistency in findings. Given the plethora of factors associated with fatigue, clinicians may need to take a multidisciplinary approach to manage this symptom in practice.

Pharmacological Interventions

Pharmacological interventions such as erythropoiesis-stimulating agents (ESA) and human growth hormone (HGH) have demonstrated small yet positive effects on fatigue. These interventions are summarized in Table 72.1.

Table 72.1 Pharmacological treatment for fatigue.

Treatment	Recommendation	Certainty of evidence	Strength of recommendation
ESAs	There is not enough evidence to recommend the use of ESAs in predialysis CKD patients, peritoneal dialysis, and kidney transplant recipients for the symptom of fatigue when present alone. If used for the management of fatigue in the setting of anemia, the evidence is insufficient to recommend an altered optimal target hemoglobin.	*Very low or absent* in CKD 1–5, PD, Tx *Low in HD* (data from one-placebo-controlled trial suggest ESAs may reduce fatigue; several trials and cohort studies suggest improvement in fatigue scores using different measures)	No recommendation: patients with CKD 1–5, PD, Tx Weak: patients on HD
Growth hormone	We suggest that the certainty of the evidence for growth hormone replacement to manage fatigue is so low that a recommendation regarding use in clinical practice is too speculative.	*Very low or absent* in CKD 1–5, PD, Tx *Very low or absent in HD* (data from small trials suggest growth hormone may improve health-related quality of life, including symptoms of fatigue)	No recommendation
L-carnitine	We suggest that the certainty of the evidence for L-carnitine to manage fatigue is so low that a recommendation regarding use in clinical practice is too speculative.	*Very low or absent in CKD 1–5, PD, Tx* *Very low in HD* (data from two small trials suggest L-carnitine may improve fatigue)	No recommendation
Antidepressants	We suggest that the certainty of the evidence for antidepressants to fatigue is so low that a recommendation regarding use in clinical practice is too speculative.	*Very low or absent* (evidence from a single trial was not robust to data missingness to suggest change in fatigue with sertraline therapy)	No recommendation

ESA - erythropoietin-stimulating agents; CKD - chronic kidney disease; PD - peritoneal dialysis; Tx - transplant; HD - haemodialysis.
GRADE assessment of the certainty of the evidence: High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different* is low. Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different* is moderate. Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different* is high. Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different* is very high. **Substantially different = a large enough difference that it might affect decision-making*.

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Erythropoiesis-stimulating Agents

ESAs, such as epoetin alpha or darbepoetin, are typically prescribed for anemia management in CKD. Treatment of anemia has demonstrated an improvement in symptoms contributing to health-related quality of life, including fatigue. In patients with CKD and with diabetes, a reduction in fatigue was seen in patients who received darbepoetin [55]. Only one randomized controlled trial (RCT) has compared those receiving ESAs to a placebo group with relation to fatigue. In this study patients treated with ESA to a low Hb target (range 9.5–11.0 g/dl) and a high Hb target (range 11.5–13.0 g/dl) had higher improvement in fatigue scores compared to those in the placebo group (22%, 26%, and 2%, respectively) [56]. One study comparing subcutaneous and intravenous ESA in patients naïve to ESAs found moderate to large improvements in fatigue for both (11%, effect size = 0.36; 19%, effect size = 0.57, respectively). Another study with ESA-naïve patients demonstrated substantial reduction in fatigue of 23% and 25% after reaching a hematocrit of 30% [57, 58]. Studies involving patients already receiving ESA treatment showed less pronounced but improvements in fatigue nevertheless [59]. A study comparing EPO and DAR (darbepoetin alfa) showed that vitality scores increased significantly after switching to DAR from EPO in patients with an Hb increase of 1 g/dl and those with Hb > 10.0 g/dl at follow-up [60]. Overall, greater improvement in fatigue scores were shown for patients with a lower baseline Hb level. However, because the use of ESAs is also associated with a substantially increased risk of stroke, the use of ESA purely for fatigue management is not recommended [61].

Growth Hormone

In the general population, treatment with HGH has been reported to improve physical functioning and vitality [62]. In CKD, however, there is only limited evidence. Early proof-of-concept studies suggested reduced protein catabolism may result in nutritional improvements, but larger studies have had more modest results. In one small study comparing controls and patients treated with HGH, the authors found higher lean body mass and serum albumin levels after 6 months of treatment. Interpretation is limited, however, by the high loss to follow-up rate (>50%) [63]. In a larger study of 712 patients randomized to placebo or HGH, neither objective measures of lean body mass or serum albumin levels, nor subjective measures such as health-related quality of life (HRQOL) and exercise capacity improved over the 20-week follow-up period, with recruitment challenges leading to early study termination [64].

l-Carnitine

Although the effects of intravenous L-carnitine have been examined in the hemodialysis population in many studies [19], direct effects on fatigue are not well-studied. Two RCTs have demonstrated that L-carnitine significantly improves fatigue compared to the placebo group in patients on hemodialysis [65]. However, these RCTs were small and thus the resulting evidence is considered weak.

Antidepressants

Antidepressants have been postulated as treatments for those with chronic fatigue because of their effect on lowering inflammatory mediators such as IL-6, and because of the close relationship between fatigue and depression. One study found selective serotonin reuptake inhibitor (SSRI) treatment was associated with reduced levels of IL-6 in patients on hemodialysis [66]. Direct evidence of the effect on fatigue scores was not measured. In a second study, sertraline was not clearly associated with a change in the energy/vitality subscale of Short Form 36 Health Survey.

Methylphenidate

A number of studies in the cancer population have reported improved fatigue in patients prescribed low-dose short-acting methylphendidate [67]. No trials in the CKD population have been done and therefore the effectiveness remains unknown. Disadvantages of methylphenidate, of importance to the CKD population, include reduced appetite and sleep quality.

Nonpharmacological Treatments

Studies examining nonpharmacological interventions such as exercise and acupoint stimulation have shown some promising results. These interventions are summarized in Table 72.2.

Frequent Dialysis

More frequent hemodialysis sessions (six times per week) have shown to improve HRQOL and time to recovery compared to the conventional (three times per week) regimen [69]. On average, patients who received more frequent dialysis recovered an hour earlier than those who received usual care.

Physical Activity

Physical activity may help improve fatigue through various mechanisms. Regular exercise may improve fatigue through

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Table 72.2 Nonpharmacological treatments for fatigue.

Treatment	Recommendation	Certainty of evidence	Strength of recommendation
Frequent nocturnal dialysis	There is not enough strong evidence to make recommendations. However, for those for whom this treatment is relevant and feasible, patients may reasonably choose to or not to receive more frequent, nocturnal dialysis.	*N/A in CKD 1–5, Tx*	Weak: patients on HD No recommendation: patients with CKD 1–5, PD and Tx
Exercise (aerobic, resistance training)	There is not enough evidence to recommend exercise in predialysis CKD patients and kidney transplant recipients to improve fatigue. We suggest that patients on hemodialysis may reasonably choose to or not to do light to moderate aerobic or resistance training exercise based on the limited evidence that it is associated with reduced fatigue scores. For patients on peritoneal dialysis, current evidence does not support exercise for fatigue, but they may experience an improvement in overall quality of life.	*Very low or absent in CKD 1–5, Tx* (data from systematic review suggest that exercise may improve fatigue across the spectrum of CKD, but outcome was limited to muscular strength and overall quality of life) *Very low in HD* (data from small trials suggest that intradialytic, low-intensity ergometric cycling, and resistance training may improve fatigue) *Very low* in PD (data from systematic review suggest possible increase in quality of life, but not necessarily for fatigue)	Weak: patients on HD No recommendation: patients with CKD 1–5, PD and Tx
Relaxation and stretching (yoga, progressive muscle relaxation, simple stretching)	We suggest that the certainty of the evidence for relaxation and stretching activities such as yoga, progressive muscle relaxation, and simple stretching to manage fatigue is so low that a recommendation regarding use in clinical practice is too speculative.	*Very low or absent in CKD 1–5, Tx* Very low in HD, PD (data from small trials using different fatigue measures suggest relaxation and stretching activities may improve fatigue)	No recommendation
Reflexology, stimulation of acupoints (acupressure, acupuncture)	We suggest that the certainty of the evidence for reflexology massages, acupressure or acupuncture to manage fatigue is so low that a recommendation regarding use in clinical practice is too speculative.	*Very low or absent* in CKD 1–5, PD, Tx *Very low in HD* (data from small trials using different fatigue measures suggest that acupuncture, acupressure, and reflexology may improve fatigue)	No recommendation
Cognitive behavioral therapy	We suggest that the certainty of the evidence for cognitive behavioral therapy to manage fatigue is so low that a recommendation regarding use in clinical practice is too speculative.	*Very low or absent* in CKD 1–5, HD, Tx *Very low* in PD (data from one trial suggests improvement in fatigue)	No recommendation

CKD - chronic kidney disease; Tx - transplant; HD - harm-dialysis; PD - peritoneal dialysis.
GRADE assessment of the certainty of the evidence [68]: High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different* is low. Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different* is moderate. Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different* is high. Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different* is very high. **Substantially different = a large enough difference that it might affect decision-making*.
Source: Based on Hultcrantz et al. [68].

its anti-inflammatory effects [70]. Aerobic exercises such as cycling and walking have been shown to improve fatigue in both the peritoneal dialysis and hemodialysis populations [71–73]. Low to moderate intensity strength training and flexibility exercises have also demonstrated improvement in fatigue [74–76]. Strength training may increase muscle strength and physical function [8]. In a study comparing aerobic and strength training exercises, both exercise types improved quality of life but only aerobic exercises (low intensity ergometric bicycle) decreased fatigue in patients on hemodialysis [77]. In a systematic review of physical activity in peritoneal dialysis, traditional

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aerobic exercises such as cycling, walking and running, tai-chi, and resistance training demonstrated inconsistent benefits on fatigue [78]. A few trials in predialysis and kidney transplant populations also showed that exercise led to improvement in factors related to fatigue such as HRQOL, physical capacity, and muscle strength [79–82]. One study found a significant slower disease progression that may prevent onset or severity of fatigue. While the effects of exercise – regardless of type – seem promising for aspects of quality of life, if not specifically fatigue regardless of stage of CKD, many of the studies are confounded by high drop-out rates, interventions, and short follow-up periods [83]. Few, however, demonstrate harm arising from incorrect prescription of exercise, excessive muscular fatigue or cardiac stress, and thus a recommendation for a modest increase in exercise is likely advisable despite the weak evidence.

Acupoint Stimulation

Reflexology and stimulation of acupoints have been studied as methods of fatigue management in patients on hemodialysis. Reflexology has shown to decrease fatigue [84]. It is a safe and feasible method to use in patients on hemodialysis [44]. Acupuncture, acupressure, and transcutaneous electrical acupoint stimulation have all demonstrated relief of fatigue compared to the control group [44, 85–87]. Larger RCTs are needed to verify the seemingly beneficial effects through more rigorous methods.

Relaxation

In hemodialysis, variations of stretching and relaxation methods such as yoga and progressive muscle relaxation have demonstrated positive results for fatigue and overall quality of life [74, 87–90].

Education and Cognitive Behavioral Therapy

One RCT reported lower fatigue following an educational intervention increasing illness knowledge in the hemodialysis population [91]. In patients on peritoneal dialysis, cognitive behavioral therapy has been found to decrease fatigue and cytokine levels [92]. The widespread uptake of educational and cognitive behavioral interventions is limited by a need for specialist trained staff to administer the intervention(s), the time commitment required from the patient for both the intervention and the homework, and the need for relatively high levels of language fluency and comprehension.

There is limited evidence for interventions to improve fatigue in any stage of CKD. For the dialysis population, there needs to be more rigorous RCTs to confirm the promising effects that have been demonstrated in smaller, shorter studies. More research involving predialysis patients and kidney transplant recipients is required to prevent fatigue in patients in earlier stages of CKD and help manage patients' lives after transplant. Treatment for patients experiencing fatigue should be a multidisciplinary approach. Before suggesting treatment, clinicians should take time to monitor levels of fatigue and assess the different factors that may be contributing to their patients' experience of fatigue, as it may differ from patient to patient.

Patient Experience of Fatigue

When considering strategies to manage fatigue, it is important to understand patient experiences, preferences, and perspectives. Fatigue is a critically important symptom for patients across all stages of CKD who identify fatigue as one of the most intrusive symptoms. Patients with CKD stages 2–4 have described their fatigue as "sudden moments without having any energy and without being able to do anything" [3]. The experience of fatigue for patients in different stages of the disease may differ, but it is clear that patients are burdened with this symptom on a day-to-day basis. Physical fatigue is common to all patients, but patients on hemodialysis seem to describe a persistent and severe physical and mental fatigue that manifest in all aspects of their lives [27]. Postdialysis leaves patients feeling like they will "collapse" and that they are "worn out" momentarily after treatment. However, patients have reported the limitations and frustrations caused by the constant need to rest due to the general fatigue they experience throughout the week. Simple, everyday activities such as walking to a taxi, getting groceries out of the car, remembering names of people, and seeing family members become difficult [20, 93]. Prioritizing aspects of fatigue that are important to patients may help to identify effective interventions.

Furthermore, patients with CKD have previously expressed their desire for treatment and strategies to manage their condition through lifestyle changes such as diet and exercise, rather than pharmacological options [94]. Similarly, exploring nonpharmacological interventions may be more aligned with patient preferences and needs regarding fatigue.

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Conclusions

Fatigue is an intrusive and debilitating symptom for patients with CKD. It is associated with low quality of life, cardiovascular disease, and mortality. RCT evidence to provide evidence of high certainty to support a specific method of treatment to manage fatigue remains lacking. Current treatment for fatigue should be based on known and perceived benefits for overall wellbeing, patient preferences, and safety.

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Depression

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Introduction

Major depressive disorder (MDD) is defined as a clinical syndrome that lasts for at least 2 weeks whereby the individual experiences depressed mood or anhedonia, and at least five symptoms from the criteria listed in the Diagnostic and Statistical Manual Criteria, Fifth Edition (DSM-5) [1]. MDD is common among patients with chronic kidney disease (CKD) and end-stage kidney disease (ESKD), more so than in other chronic conditions, and is associated with a range of adverse clinical outcomes [2–4]. Depression contributes to functional impairment, decreased quality of life (QoL), and poor adherence among patients with ESKD [5–7]. It is therefore imperative to identify and treat depression in this population. However, as will be discussed further in this chapter, depression is underdiagnosed and undertreated in this population, as only a small proportion of patients receive adequate treatment for it [8]. For example, a prospective observational study of 98 patients receiving hemodialysis found that 26% of the sample met the DSM-5 criteria for depression, however only 23% of these cases identified to experience depression were provided with interventions to treat their depressed symptoms [4]. In the majority of patients, depressed symptoms do not spontaneously improve over time without treatment, and in a large proportion of patients they worsen [9–11]. There are added difficulties in the assessment of depression in these populations due to the overlap in physical symptoms between depression and uremia [12]. There have been very few clinical trials conducted in this population to determine the safety and efficacy of pharmacological and non-pharmacological treatments [13].

It is not known whether depression in patients with CKD is different from depression that is seen in individuals without a comorbid chronic medical condition, and in particular whether depressive symptom severity and the efficacy of treatment is modified by decrements in kidney function. It is also not currently known whether the treatment of depression in CKD requires any modifications to the types of treatments used to treat depression in the general population. Across the trajectory of ESKD, treatment and disease-related factors may trigger depression, and this population experience some burdens that are different to other chronic conditions. In the early stages of CKD, the realization and acceptance of the diagnosis of CKD, changes to lifestyle and identity, fear and uncertainty regarding treatment options and their prognosis, and difficulties navigating the healthcare system may cause significant distress [14]. Kidney transplantation, which is associated with the best clinical outcomes for patients with ESKD, comes with significant burdens, including life-long immunosuppression therapy, associated side effects, and ongoing medical evaluation and monitoring [15, 16]. Kidney transplant recipients experience fear relating to the longevity of their transplant, and for those who experience graft failure, the commencement or return to dialysis can be devastating [15, 16]. Due to shortages in the availability of organs for transplantation, most patients with ESKD, with access to renal replacement therapy, receive hemodialysis [17]. Dialysis is associated with a time-consuming, painful, and often uncomfortable treatment regime that is associated with significant lifestyle disruption, and physical and neurocognitive symptoms including changes to cognition and appetite, anemia, nausea, vomiting, fatigue,

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and shortness of breath [18]. Patients on dialysis are also required to manage a complex diet and fluid regimen. Dialysis can also impact on self-esteem, social functioning, identity, and a decreased sense of self-worth [14, 19].

The following sections will discuss the definition of depression, the prevalence of depression among patients with CKD and ESKD (dialysis and transplant), risk factors and correlates, the diagnosis of depression, evidence regarding the impact of depression on clinical outcomes, evidence-based treatments for depression in this population, and finally patient and family caregiver perspectives on the impact of depression among patients with CKD and ESKD.

Definition

The DSM-5 and the International Classification of Diseases (ICD) ICD-10 are the most widely used diagnostic criteria in both clinical practice and research. While the criteria are similar, most epidemiological studies have used the DSM-5 framework. A diagnosis of MDD, according to the DSM-5, requires at least five of nine depressive symptoms to be present during the same 2-week period and represent a change from previous functioning [1]. The symptoms include (i) depressed mood most of the day, nearly every day, (ii) loss of interest or pleasure in almost all activities, (iii) significant weight loss, weight gain or change in appetite nearly every day, (iv) insomnia or hypersomnia nearly every day, (v) psychomotor agitation or retardation nearly every day, (vi) fatigue or loss of energy nearly every day, (vii) feelings of worthlessness or excessive or inappropriate guilt nearly every day, (viii) poor concentration or indecisiveness nearly every day, and (ix) recurrent thoughts of death, suicidal ideation, intent or suicide attempts. At least one of the five symptoms must include depressed mood or loss of interest or pleasure. To meet criteria for a depressive episode the symptoms must cause significant distress or impairment in social, occupational or other areas of functioning. The diagnosis is excluded if the symptoms are attributable to the use of a substance or another medical condition or psychiatric diagnosis. Persistent depressive disorder (PDD) is defined as a more pervasive but less severe depression that is present for at least 2 years [1]. To meet criteria for PDD, individuals have depressed mood for most days for at least 2 years, and the presence of two or more of the following symptoms while depressed: (i) poor appetite or overeating, (ii) insomnia or hypersomnia, (iii) low energy or fatigue, (iv) low self-esteem, (v) poor concentration or difficulty making decisions or (vi) feelings of hopelessness. An individual must not have been without these symptoms for a period of longer than 2 months.

The ICD-10 criteria for a diagnosis of a depressive episode requires four or more of 10 symptoms, present for at least 2 weeks [20]. The 10 symptoms listed include depressed mood, loss of interest and enjoyment, reduced energy leading to increased fatigability and diminished activity, reduced concentration and attention, reduced self-esteem and self-confidence, ideas of guilt and unworthiness, bleak and pessimistic views of the future, ideas or acts of self-harm/suicide, disturbed sleep, and diminished appetite. Symptoms must include two or more of depressed mood, anhedonia or energy loss. A mild episode must include four of the 10 symptoms and at least one of depressed mood, anhedonia or energy loss. A moderate episode requires six or seven of the 10 symptoms, whereas a severe depressive episode is defined by the presence of at least eight symptoms. The ICD-10 also includes a definition of a melancholic subtype of depression, called somatic syndrome. A formal diagnosis of somatic syndrome in the ICD-10 requires four or more of the following eight symptoms: marked loss of interest or pleasure, loss of emotional reactivity, waking early in the morning, 2 hours before the usual time, feeling more depressed in the morning, evident psychomotor retardation or agitation, marked loss of appetite, significant weight loss (5% or more in the past month), and loss of libido.

Epidemiology

It is estimated that the 12-month prevalence of MDD is about 7% in the general population and 10% for any mood disorder [2]. The prevalence has been shown to be 1.5–4 times higher among patients with major chronic illnesses than the general population, and even higher among patients with ESKD compared to other chronic conditions [21]. This may be due to disease-related factors including the progressive nature of CKD and the unpredictable course of the illness. Other proposed reasons include treatment-related factors such as the high medication burden among patients with CKD, the impact of dialysis on QoL, and difficulties in accessing transplantation. Risk factors for depression among patients with CKD are discussed in the following section.

Studies of patients with CKD and ESKD have identified vastly different estimates of the prevalence of depression. The difficulty determining the prevalence of depression among this population may be due to the great heterogeneity in the characteristics and treatments of the populations included in these studies, as well as the use of different screening and assessment tools to diagnose depression or assess the severity of depressive symptoms. Only a minority of patients with CKD have reached ESKD, and those with CKD have a range of different kidney diseases [12]. The

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severity of the disease and symptom burden that patients experience varies greatly depending on the cause of their disease and their associated comorbidities [18]. Most of the studies that have assessed the prevalence of depression are limited to patients receiving dialysis treatment.

The assessment of depression among patients with CKD can also be challenging due to the overlap between somatic symptoms of depression and many of the symptoms of uremia which occur with severely reduced kidney function [12]. For example, sleep disturbance, loss of appetite, fatigue, and gastrointestinal disorders are symptoms of both uremia and depression. The use of self-report tools for the assessment of depression may therefore lead to inflated estimates of the rates of depression. The diagnosis of depression using clinician interview is therefore the gold standard and will be discussed below in a section on Diagnosis. The prevalence of depression among CKD populations has primarily been studied using self-report assessment tools. Various tools have been used, thereby utilizing a range of different definitions of depression and cut-off points [22]. Moreover, many studies have used tools that have not been validated in the study population of interest.

Prerenal Replacement CKD Populations

The majority of patients with kidney disease are diagnosed with CKD, rather than ESKD. The patients with CKD stages 1–5 are extremely heterogeneous, with varying causes of kidney disease and differences in their residual kidney function. Very little is known about depression in general in this population [12]. The prevalence of MDD in patients with CKD who are not yet on renal replacement is not known but is likely to vary substantially within this group. The prevalence rates that have been reported using self-report questionnaires range from 7% to 47% [23, 24].

Hemodialysis Populations

The Dialysis Outcomes and Practice Patterns Study (DOPPS) assessed depression using both a clinician-rated and a self-report tool in an international, multicenter study of 9382 hemodialysis patients from 12 countries [8]. This study determined an overall prevalence rate of 14% for clinician-diagnosed depression, while the prevalence of depression determined by self-report measures was 43%. This study identified a wide range in depression rates across countries, ranging from 2% in Japan to 22% in the United States, using the clinician-rated assessment [8]. However, there were no differences compared to the whole sample using the Center for Epidemiological Studies Depression Scale (CESD) self-report assessment, leading the authors to conclude that cultural attitudes and practices in the diagnosis of depression may explain these differences among countries. These findings may also reflect differences in what patients feel is appropriate to report to an assessor in various countries. Single-center studies using structured clinical interviews report consistent estimates of the prevalence of depression as 25–30% among hemodialysis patients in the United States [25–27].

Peritoneal Dialysis Populations

Compared to studies assessing depression among hemodialysis populations, there are limited studies among individuals receiving peritoneal dialysis and the available studies involve relatively small samples of patients. A study of 66 adult peritoneal dialysis patients from three units in the United States found that a third of their sample had depressive symptoms [28]. A study of 124 patients on peritoneal dialysis from a single center in Turkey found that the prevalence of depression was 25.8% in their sample using the Beck Depression Inventory (BDI) [29].

Kidney Transplant Populations

The studies assessing the prevalence of depression among kidney transplant populations are predominately small single-center samples. Depression has primarily been measured by symptom levels rather than diagnosable depressive disorders among kidney recipients. A recent meta-analysis found that the pooled estimate of clinically significant depressive symptoms was 27% [30]. Recipients of a kidney transplant risk of an interview-based diagnosis of depression has been shown to be lower compared to patients with ESKD, although it remains higher than the prevalence in the general population [30]. Arapaslan et al. assessed a range of psychological disorders among 40 kidney transplant recipients during their routine follow-up appointments, held on average 5 years post-transplantation [31]. Using a structured clinical interview, 22% of the randomly selected sample were found to have MDD, and anxiety disorders were identified in 15% of the sample [31]. In a large cross-sectional study, symptoms of depression were reported by 22% of the 850 transplant recipients [32]. Dobbels et al. assessed the insurance claims through Medicare of 48 000 kidney transplant recipients between 1995 and 2003, and found that the cumulative incidence of depression increased from 6.74% to 12.9% over the first 3 years after transplantation [33]. However, another study found that self-reported symptoms of depression decreased in the first 5 years after transplantation [32]. More research is needed to understand the trajectory of depression after transplantation, including number and duration of episodes and risk for relapse [34].

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Pediatric Populations

Few studies have explored the prevalence of depression in pediatric populations with CKD. Using the Child Depression Inventory, a study of 28 children and adolescents with CKD found that these participants had a higher frequency of depressive symptoms compared to healthy controls [35]. In a study of 23 adolescent transplant recipients, depressive symptoms, assessed using the BDI, were found to occur in 17.4% of participants [36].

Risk Factors for Depression in CKD Populations

The risk factors and correlates for depression in patients with CKD can be divided into biological (inflammation), demographic (e.g. age, gender), psychosocial (e.g. social support), and cognitive factors (e.g. control expectancies and illness representation). Risk factors that have been associated with depression in patients with ESKD include younger age, female gender, white race, longer duration of dialysis, and comorbid conditions such as diabetes, coronary artery disease, cerebrovascular disease, and peripheral vascular disease [29, 37]. For patients with CKD, the risk factors are slightly varied, including younger age, female gender, minority ethnicity, lower education, lower family income, unemployment, hypertension, smoking status, diabetes, and coronary artery disease [4, 7, 23, 31, 38, 39]. However, lower socioeconomic status (SES) and comorbid conditions have been associated with higher prevalence of depression in the general population and therefore some risk factors may not be specific to CKD [15, 40, 41]. The shared risk factors for CKD and depression are depicted in Figure 73.1.

Biological risk factors associated with depression in the CKD population include the immune system, inflammatory pathways, disturbances of the hypothalamic pituitary axis and changes in the parasympathetic and sympathetic nervous systems [1, 43, 44]. Inflammation is particularly relevant to CKD and depression though studies have considerable heterogeneity [21, 34]. Pro-inflammatory cytokines have been found in higher concentrations in those with depressive symptoms and there is evidence to suggest they play a role in pathophysiological metabolism, neuroendocrine function, synaptic plasticity, and behavior [43]. CKD is often considered a pro-inflammatory state with increased concentration of markers and oxidative stress which may relate to the higher than expected rates of cardiovascular disease and other causes of increased mortality [45–48]. It is possible that this inflammatory connection could also partly explain the high rates of depression in the CKD population [5]. Additionally, in a recent cross-sectional survey of 533 individuals, Jhee et al. concluded that vitamin D deficiency was an independent confounding factor in CKD patients with depression [49]. Vitamin D is a distinctive neurosteroid hormone present in many areas of the brain which have been implicated in the pathophysiology of depression [40]. This may also partly explain the high prevalence in patients with CKD as it is well known that the blood level of vitamin D is low in this population [49].

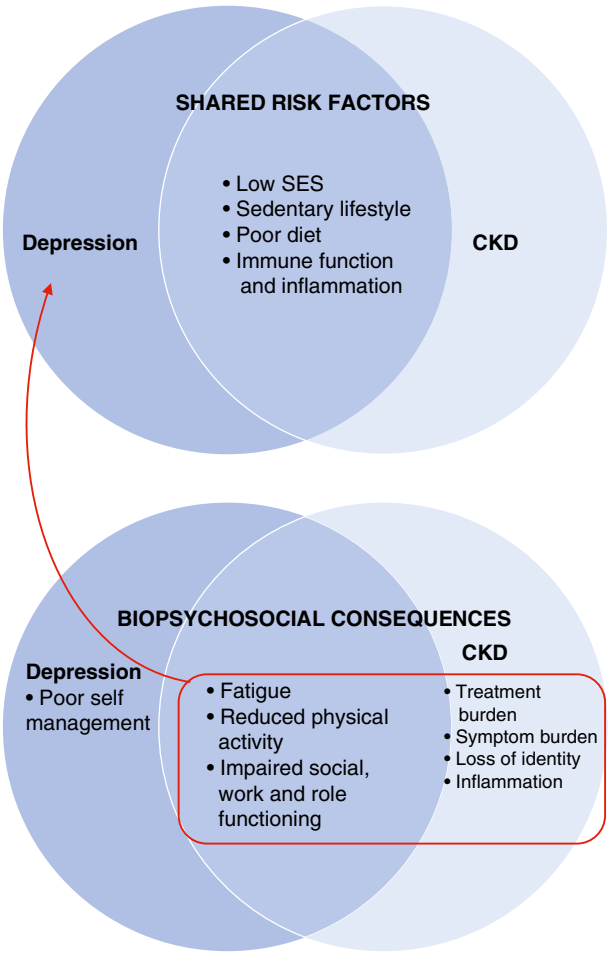

Figure 73.1 Shared risk factors and biopsychosocial consequences of CKD and depression. *Source:* Adapted from Bautovich et al. [42].

Psychosocial factors including social support, personality attributes, cognitive appraisals, and perceived stress may be associated with depression [10]. Personality attributes and cognitive appraisals have shown to have a particularly large effect [10]. Beck's cognitive triad theory describes a cognitive model of vulnerability to developing depression when faced with a stressful event, such as diagnosis of a chronic illness, which is characterized by negative views of the self, world, and future [50]. A negative view of the self leads one to view loss as personal, leading to self-loathing, self-criticism, and feelings of inadequacy and worthlessness. Negative views of

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the world lead one to view loss to be pervasive, and the world as unfair, harsh, and hostile. Others are viewed as being uncaring, unable to help, and superior. Depression is also characterized by a negative view of the future, where loss is seen as permanent, the future is predicted to be bleak, pointless, and there is a sense of hopelessness that their circumstances will change or improve. Relating to the perception of loss, cognitive factors such as health locus of control, illness representation, negative illness schemas, and illness intrusiveness have also been associated with increased risk for depression in CKD [11, 13, 17–19, 24]. One study found that patients with ESKD who perceived greater consequences as a result of their health status and less personal control over their illness were more likely to endorse symptoms of depression [11]. Moreover, research suggests that negative illness schemas are associated with increased depression in ESKD and that positive illness schemas mediate the relationship between social support and depression in this population [24]. Schemas represent the cognitive generalizations that guide the processing and interpretation of information that is relevant to the self [51]. Studies by Chan et al. [45, 52] in dialysis patients identified a relationship between cognitive factors, depression, and QoL. Such cognitive factors included the perceived burden of kidney disease, a sense of loss related to kidney disease, and self-efficacy.

Studies examining the role of coping styles in depression in this population have had inconsistent findings. One study found that coping styles associated with seeking information in order to manage health problems was associated with reduced risk for experiencing ongoing or increasing depression symptoms after kidney transplantation [53]. However, other studies have not found a significant association between either maladaptive coping strategies or adaptive coping strategies and depression [54, 55]. Given the small number of studies assessing the impact of coping styles, it remains unclear whether this is a risk factor for depression.

Actual and perceived lack of social support have also been identified as risk factors for depression across chronic health conditions, including patients with ESKD. In a study of 109 dialysis patients from the United States, risk factors for depression were explored, including participants' perceptions of their illness, disease severity, and level of social support [51]. In this study, negative illness perceptions were associated with depression, whereas positive perceptions were negatively associated with depression. Similarly, access to social support was associated with a positive illness schema, and lower levels of social support were shown to be associated with higher levels of depression. Social support was significantly related to depression, independent of positive illness schemas, suggesting that a low level of social support is a risk factor for depression. In studies of kidney transplant recipients, poor social support has been found to increase depression risk, with both the lack of available support persons and poorer perceived quality of the emotional and tangible support having been shown to be important factors [32, 37, 46, 56]. Researchers have suggested that perceived social support in patients may encourage positive psychological adjustments to life with CKD and associated losses in wellness, lifestyle, independence, autonomy, and identity [5, 9, 57, 58].

Low SES is a risk factor for depression [59]. Low SES is also a risk factor for diabetes and cardiovascular disease, adverse health behaviors, and poor management of health conditions [41]. Therefore, low SES is a shared risk factor for both depression and CKD [60]. In kidney transplant recipients, unemployment and personal financial stress post-transplant have consistently been found to increase depression risk [32, 37, 61].

Among patients with ESKD and the general population, the strongest risk factors for a future episode of depression are a family history of depression and a past history of depression symptomatology [62, 63]. For example, across all types of organ transplant recipients, a pre-transplant history of mental health disorders, including depression and anxiety, is the strongest risk factor for development of such disorders post-transplant [57]. Thus, screening for psychological and family history could provide important information, among other risk factors, to encourage screening of depression symptoms.

Anxiety is often comorbid with depression in the general population [43, 64]. Anxiety is an important consideration because it may contribute to the onset of depression and may also exacerbate symptoms of depression [37]. Anxiety has an estimated prevalence rate of 38% (12–52%) among dialysis patients, however there is even less research on anxiety in this population compared to that of depression [65]. A cross-sectional study of 119 renal transplant recipients in Panama found that the prevalence of anxiety was 15.1% [37]. This study also found that the presence of an anxiety disorder was significantly and independently associated with depression symptoms, as was increasing age and a lower educational attainment [37]. One study found that patients with ESKD who were receiving renal replacement therapy present with a higher level of anxiety compared to healthy controls and a lower level compared to patients diagnosed with breast cancer [66]. They found that the severity of anxiety did not differ by end-stage renal disease (ESRD) treatment type. This study also found that patients with a high level of trait anxiety (a relatively stable tendency toward anxiety in response to the anticipation of a threat) had a more severe anxiety-induced state (which depends on external factors) when faced with advanced somatic disease [66]. Anxiety may also be difficult to detect due to similar difficulties distinguishing symptoms of

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anxiety from symptoms of CKD. Common symptoms of anxiety include dizziness or lightheadedness, racing heart, shakiness/unsteadiness, indigestion, numbness/tingling, nervousness, avoidance, hand trembling, difficulty breathing, hot/cold sweats, muscle tension, a fear of losing control, and a fear of death [65].

The Impact of Depression on CKD Outcomes

Clinical depression and depressive symptoms bring many disadvantages, including poor psychosocial and medical outcomes in patients with CKD and ESKD. Patients are at increased risk for adverse clinical outcomes including mortality, hospitalization, poor adherence to treatment, and decreased QoL [8, 38, 49, 56, 60, 67].

Mortality and Morbidity

A strong and statistically significant association exists between depression status and risk of all-cause mortality in patients with all stages of CKD, regardless of sex or age [49, 62]. A study by Tsai et al. found that those with a higher depressive symptom burden at baseline (BDI, score > 11) are more likely to reach the endpoint of ESKD or death by 25.2 months (±11.9 months) as compared to those with a lower BDI score [7]. Similarly, those with more depressive symptoms also had a faster decline in their estimated glomerular filtration rate (eGFR), more hospitalization, and were more likely to start dialysis at a higher eGFR [7]. These findings of individual studies have been confirmed by a meta-analysis conducted by the Cochrane Renal and Transplant Group, which shows a strong association between depression and all-cause mortality at a relative risk of 1.59 with moderate levels of heterogeneity in the studies [67]. While the meta-analysis adjusted for stage of CKD, length of dialysis, method used to diagnose depression, and point in time when depression was assessed, the association was weaker when studies controlling for cardiovascular disease were taken into consideration [67]. One suggested mechanism for the increased risk of death among CKD patients with depression is the presence of cardiovascular disease [22]. However, this meta-analysis found that depression consistently increased the risk of all-cause mortality, but was less certain for cardiovascular mortality specifically. The increased risk of mortality among adults with CKD was shown to be higher than for other populations, including patients with cancer, diabetes, and cardiovascular disease [67].

In a systematic review by Farrokhi et al., the authors found that the mortality risk in patients on dialysis was 1.5 times higher in the presence of depressive symptoms, independent of other confounding factors [58]. They also found that this relationship was dose dependent (the more severe the depression, the higher the risk of mortality) [58]. A meta-analysis of 27 studies across heart, liver, kidney lung, pancreas, and mixed transplants found that depression increased the relative risk of mortality by 65% and the level of risk was not affected by the type of transplant [6]. Depression also increased the risk of graft loss (censored for death), whereas anxiety was not found to significantly increase the mortality or morbidity risk [6]. Among kidney transplant recipients specifically, an association has been found between depression and adverse outcomes, with comorbid depression associated with worse graft function, graft failure, increased risk for chronic allograft nephropathy, return to dialysis or death [2, 20, 60, 65].

Suicide and Treatment Withdrawal

Another reason that patients with depression may have an increased mortality rate is due to a higher risk of suicide and withdrawal from treatment [68]. As described in the section on the definition of depression, suicidal ideation is a common symptom of depression. An early study reported very high rates of suicide among ESKD patients compared to the general population and other chronic disease populations [69]. This study appeared to have selected a sample that was high in risk factors for suicide and this sample was utilizing less efficient and adequate dialysis technology compared to those available currently [69]. More recent studies have identified much more moderate rates of suicide. In a recent study, suicide rates were found to be higher among dialysis patients compared to the general population [70]. In this study, the crude suicide rate between 1995 and 2001 was 24.2 deaths from suicide per 100 000 patient years [70].

There is also confusion regarding the distinction between treatment withdrawal and intended death by suicide [47]. Patients with suicidal ideation may attempt suicide through nonadherence to their dialysis, diet, fluid or medication prescription or by altering their vascular access [48]. Alcohol and drug dependence and recent hospitalization for mental illness were found to be strong risk factors for patient death by suicide [70]. This same study found that the populations who withdraw from treatment are different from those who die by suicide. The risk of death by suicide was highest in the first 3 months after the initiation of dialysis, whereas the likelihood of withdrawal from dialysis was highest for the first year of dialysis therapy [70]. Older age and recent hospitalization were stronger predictors of treatment withdrawal than death by suicide [70].

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Medical complications, diabetes, cerebrovascular disease, and dementia have been associated with the decision to withdraw from treatment [47, 71].

It has been estimated in these studies that approximately 20% of patients on dialysis choose to discontinue treatment [47, 71]. Withdrawal from dialysis is the second most common cause of death among dialysis patients after cardiovascular disease [38]. There is considerable cultural variation in the rates of treatment withdrawal such that higher rates have been identified among Caucasian patients compared to Asian and African American patients in the United States [72]. A large international study by Lopes et al. found that patients receiving hemodialysis who met criteria for depression or depressed symptoms were shown to have a higher rate of treatment withdrawal [73]. However, this study relied on medical records and nonstandardized assessment tools to determine participants' depression diagnosis or frequency of depressive symptoms. Subsequently, a study by McDade-Montez et al. estimated that the risk of withdrawing from dialysis was 43% higher for participants who scored one standard deviation above the mean on the BDI compared to patients who had average scores on this depression measure [74]. It is therefore recommended that patients' end-of-life treatment decisions include assessment and treatment for depression [18].

Hospitalization

Depression has been associated with increased healthcare costs, including primary, pharmacy, inpatient medical, inpatient psychiatric, and outpatient mental healthcare [35]. DOPPS was a large study with 5256 hemodialysis patients that found depression was associated with an increased risk for first hospitalization even after adjusting for time on dialysis, age, race, SES, comorbid indicators, and country [56]. Depression has also been significantly associated with other adverse medical outcomes including emergency department visits, cumulative hospital days, cardiovascular events, peritonitis, withdrawal from dialysis, and suicide [8, 29, 54, 71, 75]. Multiple other studies have investigated the association between depression and a variety of negative health outcomes in renal disease, including dialysis initiation, hospitalization rates, length of stay, and death [26, 29, 30]. Each study has noted an association between depression and hospitalization.

Adherence

Treatment nonadherence is another potential pathway through which depression may affect mortality and morbidity in patients with CKD. Treatment adherence can be quite complex for patients with CKD, requiring adherence to a weekly dialysis schedule, maintenance of peritoneal exchanges for peritoneal dialysis, dietary restrictions, physical activity, and complex polypharmacy. Depression has been identified as the most important predictor of adherence to medication prescriptions among patients on hemodialysis [75, 76]. While adherence in ESKD is challenging to quantify [12], most studies have indicated a relationship between depressive effect and laboratory and behavioral markers of poor compliance in the dialysis patient [3, 36, 53, 55]. Depressive symptoms of low motivation, hopelessness, and suicidal ideation can significantly interfere with adherence to dialysis schedule and prescribed medication as well as dietary regimens [3, 36, 55, 59]. Decreased behavioral adherence, such as skipping dialysis sessions, shortened dialysis time, and nonadherence to the prescribed diet, can have a significant effect as it has been associated with impaired nutrition, higher risk of withdrawal from treatment, and ultimately decreased survival [3, 50, 53, 59]. In a 2002 DOPPS report, a diagnosis of depression was associated with a 1.6 times increased likelihood of skipping or shortening hemodialysis sessions when controlling for other risk factors [75].

Infection

Compared to patients without depression, patients on peritoneal dialysis who endorse symptoms of depression are twice as likely to develop peritonitis [39]. Troidle and Wanick's study included 162 patients and showed that a BDI score of 11 or greater was associated with the development of peritonitis. Juergensen et al. studied a large sample of patients on chronic peritoneal dialysis and found that more than one past experience of peritonitis was associated with higher anxiety and depression scores than in patients with one or no episodes of peritonitis, although the increased depression was not statistically significant [77].

Quality of Life

Health-related quality of life (HRQOL) provides an assessment of the patient's perception of the physical and psychosocial impacts of their condition and treatment. HRQOL is significantly compromised in patients with ESKD and has been associated with increased morbidity and mortality [69]. Depression has been found to have a profound negative impact on QoL among patients on renal replacement therapy and is possibly more strongly associated to QoL than clinical and sociodemographic variables [51, 72, 74]. This is likely because patients with comorbid CKD and depression are more likely to perceive

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and rate their QoL lower due to the impact of low mood on their subjective appraisals of their functioning. Patients with depression have been found to have two- to threefold more medical symptoms compared with controls without depression, including more fatigue, cognitive difficulties, pain, sleep disturbances, sexual dysfunction, and interpersonal difficulties [35, 69]. Depression is also associated with reduced social and occupational functioning, which can cause financial difficulties and thus further impact wellbeing [25, 52].

Diagnosis

As with most chronic disease populations, depression is often underdiagnosed among individuals with CKD. This may be due to the limited resources available for clinicians to assess mental health symptoms, and complaints about somatic symptoms may not be recognized as being associated with depression due to also being associated with kidney disease. Given this overlap, it is generally recommended that the diagnosis of depression among CKD populations relies more heavily on psychological symptoms such as anhedonia, guilt, hopelessness, and suicidal ideation [44].

Clinical Examination

The clinical diagnosis of depression is based on clinical interviews including specific criteria or various self-reported questionnaires [67]. The DSM-5 is the current standard set of criteria used to diagnose mental disorders and is often used in prevalence studies of depression in CKD and ESKD [4, 62]. The DSM-5 criteria are useful for studies that use a broad definition of depression encompassing several different depressive disorders, including MDD, PDD, and depressive disorder not otherwise specified [4].

The gold standard to diagnose depression in the research setting is the clinical interview, including the Structured Clinical Interview for DSM-5 (SCID-5) [70], the Composite International Diagnostic Interview (CIDI) [76], and the Mini-International Neuropsychiatric Interview (MINI) [66]. In clinical practice, lengthy clinical diagnostic interviews might be used, but these are not currently standard practice. Self-reported questionnaires are often used in clinical and research settings for screening of depressive symptoms. The most commonly used depression screening questionnaires that have been validated for use in patients with CKD and ESKD are the Patient Health Questionnaire-9 (PHQ-9) [73], the Patient Health Questionnaire-2 (PHQ-2) [78], the BDI [27, 73], the Hospital Anxiety and Depression Scale (HADS) [64], CESD [27], and the Quick Inventory of Depressive Symptomatology Self-Report (QIDS-SR) [32]. The PHQ-9 items are shown in Table 73.1 as an example of a screening questionnaire.

Several studies have validated depression-screening questionnaires against the SCID in patients with ESKD, while only one study has validated questionnaires against SCID to screen for depression in patients with CKD [14, 16, 27, 32, 73]. However, some overlap between the somatic symptoms of depression and the symptoms related to ESKD exist (including fatigue, difficulty concentrating, difficulty sleeping, and poor appetite), therefore patients with uremic symptoms may screen positive for depression with a self-reported questionnaire [14, 16, 27, 32, 73]. Many investigators have suggested that nonsomatic or psychological symptoms of depression (e.g. dysphoric mood, guilt, etc.) distinguish depressed from nondepressed ESKD patients better than somatic symptoms [13, 16, 61]. Researchers have also proposed that focusing on more subjective indicators such as social withdrawal may better capture depression in chronic illness populations [68].

In one study that screened patients with CKD and ESKD for depression using the BDI, the authors found that the optimal cut-off scores for patients with ESKD are 14–17, whereas for patients with CKD they were the same as the general population (i.e. cut-off score of 11 or greater) [6, 27, 28, 64]. However, the inclusion of patients with CKD stages 2 and 3, who are less likely to experience symptoms related

Table 73.1 Patient health questionnaire-9 (PHQ-9).

Over the last 2 weeks, how often have you been bothered by any of the following problems (not at all, several days, more than half the days, and nearly every day?):
1) Little interest or pleasure in doing things
2) Feeling down, depressed or hopeless
3) Trouble falling or staying asleep, or sleeping too much
4) Feeling tired or having little energy
5) Poor appetite or overeating
6) Feeling about yourself – or that you are a failure or have let yourself or your family down
7) Trouble concentrating on things, such as reading the newspaper or watching television
8) Moving or speaking so slowly that other people could have noticed? Or the opposite – being so fidgety or restless that you have been moving around a lot more than usual
9) Thoughts that you would be better off dead or of hurting yourself in some way.
If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people? (not difficult at all, somewhat difficult, very difficult, extremely difficult)

Source: Based on Kroenke et al. [79].

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to kidney disease, could have influenced the results. The clinical interview remains the gold standard for diagnosing depression in patients with ESKD to distinguish overlapping symptoms. Future validation studies are needed for patients with advanced CKD and depressive disorders [67].

Screening Strategies

There are two screening strategies in patients with CKD and ESKD that are generally used: a conservative approach and an aggressive approach [14, 33]. The conservative approach is only implemented when patients display signs of depression such as social isolation, changes in mood or physical functions and/or increasing physical complaints (sleep disturbances, decreased self-care, etc.). The aggressive approach is to periodically screen all new CKD or ESKD patients for depression at key points of transition (initial evaluation, dialysis initiation, etc.) with screening questionnaires [33, 67, 78, 80]. These questionnaires can be completed during regular visits for dialysis or while waiting for appointments. However, it has also been recommended that the benefits and harms of psychiatric intervention in this population need to be evaluated before implementing screening programs [22].

Depression screening should be carried out by specific healthcare providers, such as a nurse, social worker or physician, who should be trained on a protocol for administering depression screening questionnaires [67]. Questionnaires, particularly items evaluating suicidal ideation, should be reviewed prior to patients leaving the clinic or dialysis center [67]. Patients who screen positive for depression should be referred to a qualified professional to confirm the diagnosis with a clinical interview [67]. Patients who require immediate referral to a mental health professional or emergency psychiatric services include those with suicidal ideation, plan, or intent and those with depression complicated by psychosis or mania (bipolar) [33]. A proposed pathway for assessing and managing depression in patients with CKD and ESKD is summarized in Figure 73.2.

Treatment

Despite reports of the high prevalence of depression among patients with CKD and ESKD, and the significant impact of depression on a range of important clinical outcomes, psychological conditions are undertreated in this population [44, 81]. Effective treatment of depression is likely to improve a range of outcomes for patients, as well as lead to reduced costs for the healthcare system. Systematic efforts to screen, diagnose, and treat depression need to be effectively integrated across the care pathway for patients with CKD. Psychotherapy, particularly cognitive behavioral therapy (CBT), pharmacotherapy, or a combined treatment, are the recommended first-line treatment for depression [82, 83]. However, in current practice very few patients with CKD/ESKD are assessed or treated for depression. Depression treatment has also received little attention in CKD research, with few randomized controlled trials available to inform evidence-based treatment and safety [42]. There is therefore a lack of data to inform the treatment of depression in this setting, or to suggest that treatment can improve depression or other impacted clinical outcomes [81], thus no recommendations are made based on research evidence. However, in clinical practice it is generally accepted that these strategies can be utilized safely. Given that antidepressants have been shown to work in other populations, it is generally accepted that they would work for kidney patients, as long as they can be used safely. Proposed clinical guidelines for the assessment and treatment of depression in CKD are described in Table 73.2.

Pharmacological Treatment of Depression

The main classes of antidepressants including selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), monoamine oxidase inhibitors (MAOIs), and tricyclic antidepressants (TCAs). Patients with more advanced CKD and those on dialysis or transplant have largely been excluded from large trials of antidepressant therapies among the general population and patients with cardiovascular disease [81, 84]. The clearance of antidepressant drugs or potentially toxic metabolites may be reduced in individuals with reduced kidney function and they may not be removed significantly by dialysis treatment as these medications are typically highly protein bound [83]. Drug–drug interactions are of particular concern in this population, given that patients with CKD and ESKD are typically prescribed a large number of medications, particularly individuals with complex comorbidities. Most immunosuppressive medications are metabolized by the enzyme CYP3A4 (e.g. tacrolimus, cyclosporine, sirolimus), therefore it is recommended that pharmacological treatments that interact strongly with 3A4 be avoided or used with caution among transplant recipients [85]. Drugs that inhibit or induce CYP3A4 can result in toxicity or inadequate immunosuppression and increase the risk of graft rejection. Several classes of antidepressants have cardiovascular side effects, which is problematic in this population due to the high prevalence of cardiovascular disease [44]. A range of other common adverse effects have been reported that would increase the symptom burden of CKD and ESKD [44]. Gastrointestinal side effects of immunosuppression can be

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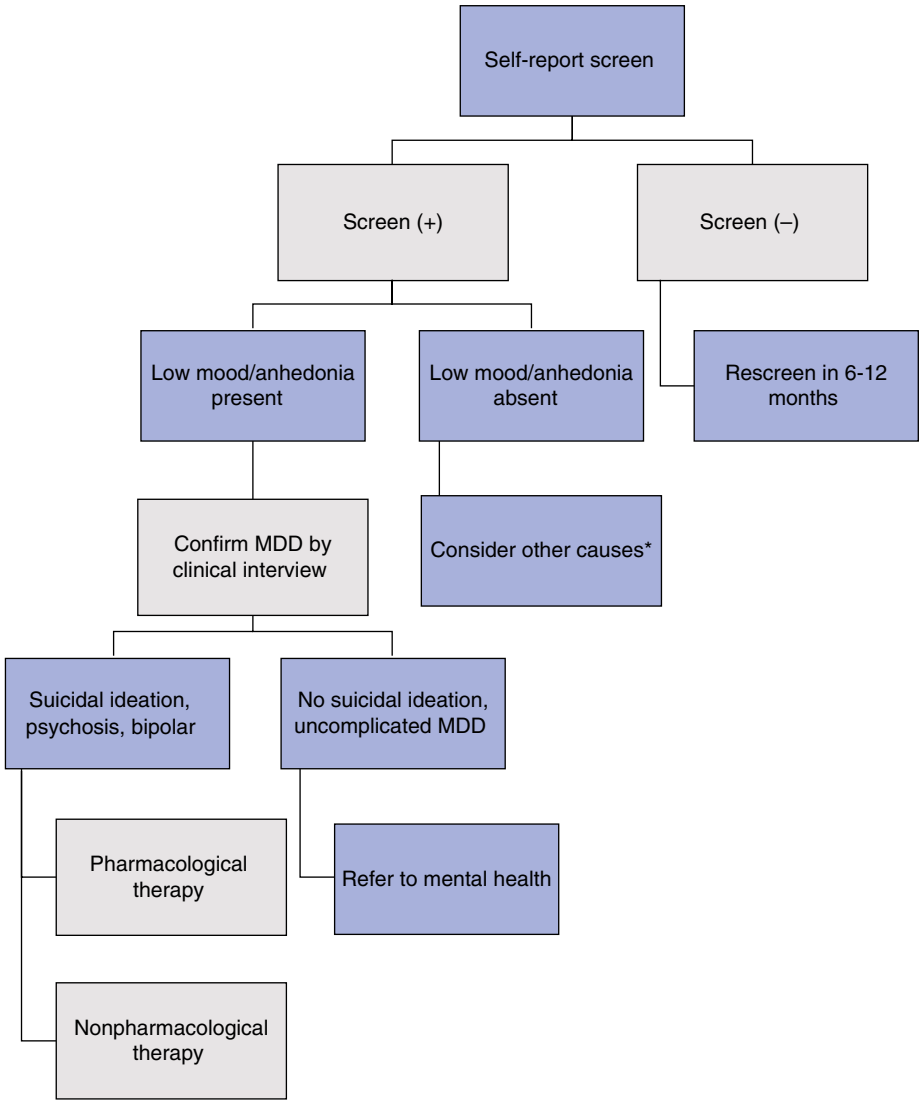

Figure 73.2 Hedayati's proposed algorithm for assessing and managing depression in patients with CKD and ESKD. *Other causes may include uremia, dialysis inadequacy, poor nutrition, cognitive dysfunction, comorbid illness, and inflammatory conditions. *Source:* Adapted from Hedayati et al. [44].

aggravated by using psychotropic medications with similar side effects, for example SSRIs and venlafaxine (a SNRI) [85]. Due to the lack of clinical trials in this population, the choice of antidepressant is based on what is known about the pharmacokinetics, drug–drug interaction effects, and the adverse event profiles of each antidepressant. Therefore greater caution is recommended in the prescription of antidepressants for patients with CKD compared to the general population [42].

While there are pharmacological trials of antidepressants with patients with CKD, these studies generally have small sample sizes, lack control groups, rarely use the gold standard assessments to diagnose depression, and the participants are not randomized to treatment [44, 81]. A recent metaanalysis conducted by the Cochrane Renal and Transplant Group included only four randomized controlled trials involving 170 patients on dialysis [13]. The metaanalysis compared SSRIs to placebo or psychological training, however the data were sparse and generally inconclusive regarding the benefits and harms of antidepressant medication [13]. This review concluded that there is not enough evidence to support the prescription of antidepressant medications in adults receiving dialysis, unless as participants in randomized controlled trials, due to the potential for increased harm. Although based on only three studies, this review also concluded that nausea may be caused by antidepressant treatment [13].

Since this review was published, the Chronic Kidney Disease Antidepressant Sertraline Trial (CAST), a randomized controlled trial involving 201 patients with stages

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Table 73.2 Clinical guidelines for depression assessment and treatment in chronic kidney disease.

- Assess for depression with face-to-face clinical interview in a private and confidential setting that encourages disclosure. Clinicians should focus on cognitive symptoms.
- Assessment of depression should be an iterative process, as patient moves between different stages of chronic kidney disease and treatment.
- Clinicians should actively monitor treatment adherence and suicide risk among depressed patients to reduce risk of poor clinical outcomes, suicide, and death, and monitor for voluntary withdrawal from treatment.
- Clinicians should seek to understand patient's preferences and attitudes toward depression treatment and seek to individualize treatment to their needs.
- Depression is best managed by a multidisciplinary support team.
- When considering pharmacotherapy for the treatment of depression, clinicians are advised to prescribe selective serotonin reuptake inhibitors, starting at low doses and frequently monitoring for side effects and adverse effects. Clinicians and patients should be aware that research regarding the efficacy and safety of antidepressant medication in this population is not sufficient to inform outcomes. Drug–drug interactions should also be monitored closely.

Source: Based on Christensen et al. [18].

3–5 nondialysis-dependent CKD, was completed to determine whether sertraline (an SSRI) improves depressive symptoms in patients with CKD and MDD [86]. After 12 weeks of sertraline treatment, the antidepressant therapy did not significantly improve depressive symptoms compared to placebo treatment [86]. These findings therefore do not support the use of sertraline to treat depression among patients with CKD not yet on renal replacement therapy. This study did find that nausea, vomiting, and diarrhea occurred more frequently in the sertraline group compared to the placebo group [86].

Given the lack of data available regarding the pharmacological treatment of depression in patients with CKD and ESKD, some nephrologists may be hesitant to prescribe their patients another medication. SSRIs are considered to be the most promising antidepressants for this patient population, based on established safety in patients with cardiovascular disease [44]. SSRIs are considered safer than MAOIs and TCAs for patients with kidney disease because they have fewer side effects and drug–drug interactions [42, 87, 88]. However, patients must make an informed decision to commence antidepressant therapy with awareness of the gaps in knowledge regarding the efficacy and safety for pharmacological treatments for depression for individuals with CKD/ESKD. Moreover, response to treatment, dose adjustment, possible drug–drug interactions, side effects, and adverse effects need to be monitored closely at each consultation. The use of antidepressant medication is supported by significant clinical expertise and experience. Despite the lack of data to guide decisions, it has been widely recommended that antidepressants be prescribed at the lowest effective doses, and that non-SSRIs be reduced by a third for kidney disease patients [87, 88]. Importantly, an increase in suicidal ideation and behavior after commencing antidepressant therapy has been shown in the first month after commencing antidepressants and must be monitored regularly [89].

Nonpharmacological Treatment of Depression

Nonpharmacological interventions, particularly CBT, are an important evidence-based treatment option for patients with depression in the general population that are requested and preferred by some patients over pharmacological interventions. In regards to the treatment of mild to moderate depression in the general population, nonpharmacological treatments have been shown to be as efficacious as pharmacological treatment and a useful adjunct to pharmacological treatment for more severe depression, with a particular benefit for the prevention of relapse [90]. Combined treatment of antidepressants and psychotherapy has not been studied in the CKD and ESKD populations. Some of the nonpharmacological interventions that have been studied in this population include adjusting the dialysis treatment regimen, exercise programs, psychotherapy (e.g. CBT), psychoeducation, music and art therapy, relaxation training, and meditation. However, nonpharmacological interventions for depression are often inaccessible to nephrologists and other healthcare providers in this setting due to limited resources [44].

Randomized controlled trials involving psychological treatments for depression in patients with CKD/ESKD have been scarce. A Cochrane Systematic Review published in 2005 was unable to identify any randomized controlled trials involving psychotherapeutic interventions for the treatment of depression among dialysis patients [91]. Psychological interventions that are adapted to the specific stressors and burdens experienced by patients with CKD and ESKD need to be evaluated. For example, dialysis-specific treatments may address fears around surgical procedures, loss of independence, changes in body image, uncertainty about health and the future, and the challenges of self-management. Some specific needs of dialysis patients that could be included in CBT could also include lifestyle disruption, feelings of loneliness and isolation due to their dialysis schedule, and the uncertainty of accessing transplantation [92]. For transplant recipients, a focus on a fear of graft failure and coping with immunotherapy would

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be required [15]. CBT is the most widely investigated psychotherapy for depression (see different types of psychotherapy at https://www.div12.org/diagnosis/depression). CBT has a focus on the maladaptive beliefs, cognitive styles, and behavioral patterns that contribute to and maintain depressive symptoms. Specific techniques included in these interventions include problem solving, skills training to better cope with the impact of the disease, behavioral activation (increasing engagement in valued activities), and cognitive restructuring of dysfunctional thoughts [50]. Targeting unhelpful illness perceptions through CBT might be an effective approach for some patients [93].

There are only two small RCTs that have studied the efficacy of CBT for depression compared to usual care among patients receiving hemodialysis. A recent randomized crossover trial adapted a CBT intervention to provide chair-side depression treatment for dialysis patients from two centers during dialysis treatment, and focused specifically on the symptoms experienced by dialysis patients [94]. Compared to the waitlist group ($n = 23$), 33 participants in the treatment first group had significantly larger reductions in scores on the BDI and Hamilton Depression Rating Scale. Among participants with diagnosed depression at the start of the study, 89% of those in the treatment group did not meet criteria for depression at the end of the treatment compared to 38% in the waitlist group. The treatment group also experienced greater improvements in QoL and reductions in interdialytic weight gain. There may be issues regarding privacy and confidentiality when providing therapy chair-side while patients are undergoing dialysis in a public space among other patients. Duarte et al. conducted a trial of group CBT led by a trained psychologist over 3 months, whereby 41 hemodialysis patients attended 12 weekly sessions and were compared to 44 patients who received treatment as usual [95]. At 9 months follow-up, the intervention group had significant improvements in the BDI, MINI, and QoL compared to the control group. Their CBT intervention included 3 months of active treatment involving self-monitoring of symptoms, cognitive restructuring, behavioral activation, relaxation training, and relapse prevention. Participants received monthly maintenance sessions for 6 months. The treatment as usual group received emotional support and guidance on their treatment. This group intervention is considered a more cost-effective treatment option to individual sessions. A limitation of this study was that patients in both the active treatment and control groups were taking antidepressant medications during the study period.

More recent studies have explored adaptations to CBT to make it more acceptable and feasible in dialysis populations. A feasibility open trial was conducted with 22 patients on dialysis using an internet-delivered CBT program [96]. This single-group open trial found clinically significant improvements in depression, anxiety, and general distress which were maintained and further improved over a 3-month follow-up period. The patients who enrolled in the trial also reported improved QoL and perceived kidney disease-related loss. This study did not find any improvements in perceived disability or kidney disease burden. Importantly, this study was highly accepted by clinicians and patients. There is increasing evidence for the effectiveness of internet-delivered CBT in reducing depression and anxiety [97], including studies in patients with other chronic health conditions [98]. This would also likely be beneficial for rural renal patients.

There are also few studies of psychotherapy interventions for depression among individuals who have received a kidney transplant. In a randomized trial conducted with 82 kidney transplant recipients [99], patients were provided with 12 weeks of individual or group psychotherapy, which focused on adaptation to treatment. A control group was also constructed, although participants were not randomized into the control arm of the trial. This trial found that the kidney transplant recipients depression symptoms reduced when compared their pre-treatment scores to post-treatment scores for both intervention groups, compared to the control group where depression symptoms increased over time. This decline in depression symptoms was maintained 12 months after both interventions among the 55 patients who completed the follow-up assessment at 1 year post-transplant. Improvement in depression symptoms was significantly greater in the individual therapy group compared to group therapy.

A randomized controlled trial examined the effectiveness of an 8-week Mindfulness-Based Stress Reduction (MBSR) group intervention among kidney, lung or pancreas transplant recipients compared to health education [100]. The intervention targeted depression and anxiety symptoms and sleep disturbance. The intervention was shown to result in significantly reduced anxiety symptoms and sleep problems compared to the health education intervention, and these benefits were sustained at 12 months after treatment. The MBSR group also saw a reduction in depression symptoms that was sustained at 12 months, but this was not significantly greater than the health education intervention.

Exercise training programs may also be promising interventions that can possibly improve physical function, QoL, and depressive symptoms. In a trial of hemodialysis patients with reduced aerobic capacity, 19 patients were randomized to an intradialytic exercise training program over a 10-month period and 14 were randomized to a control group [101]. In the intervention group, participants had a 21% increase in VO_2 max and a 39% reduction in their BDI score, which was significantly different to the control group which experienced

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no change in these measures. Levendoğlu et al. [102] evaluated the effects of a 12-week exercise program on functional capacity, mobility, walking capacity, QoL, and depression in patients on hemodialysis. This study found significant reductions in depression scores and improvements to physical and mental QoL in the intervention group. However, these studies were not conducted in patients with a diagnosis of depression. Exercise training programs may suffer from high patient dropout rates, particularly among hemodialysis patients compared to predialysis or post-transplant patients [103], possibly due to requiring frequent hospital appointments, and often suffering from fatigue and muscle weakness [104].

Given the other psychosocial risk factors for depression, it has been suggested that interventions targeting family discord, marital relationships, social support, and social participation may improve depressive symptoms [44]. Interventions directed toward caregivers or both patients and caregivers may be particularly important in home-based interventions [105, 106]. Financial support may also relieve emotional distress related to financial stressors for patients with ESKD [107].

Some research has suggested that increasing the dialysis prescription from three times weekly sessions to daily dialysis sessions improves depressive symptoms due to a reduction in physical symptoms through increased blood pressure control and improved renal clearance. An observational study showed that after a cohort of patients changed to six times weekly hemodialysis sessions, their BDI scores decreased and this was sustained at the 12-month follow-up assessment [108]. However, the efficacy of the intervention is uncertain due to the lack of a control group. The Frequent Hemodialysis Network (FHN) randomized controlled trial compared six sessions per week of in-center hemodialysis with participants undergoing the conventional three sessions per week hemodialysis [109]. This study found that patients in the frequent hemodialysis group had a significantly higher weekly standard Kt/V_{urea} compared to the conventional dialysis group, significant benefits in composite outcomes of death or change in left ventricular mass, death or change in physical health composite score, and improved hypertension and hyperphosphatemia control. However, they were more likely to require vascular access intervention and there were no significant effects on self-reported depressive symptoms. Both time on dialysis and vascular access interventions pose significant burdens and distress for patients [110–112].

Barriers to Depression Treatment

The treatment of depression in CKD and ESKD populations comes with some unique challenges and barriers. There may be reluctance among clinicians to treat depression in patients with CKD. A survey of renal clinicians from nine hemodialysis units in Pennsylvania, United States found that participants reported that they did not treat pain, sexual dysfunction, or depression in their patients. The reason for this was their belief that primary care providers were responsible for treating these symptoms [113]. Although this was a small study, this may be an important factor contributing to both the low rates of detecting and treating depression among the CKD/ESKD population and is not unique to CKD. Clinicians may also be hesitant due to the lack of data from large scale clinical trials [114].

Patient and family caregiver attitudes toward antidepressant therapy may also be an important barrier to treatment. A recent study examined the acceptance of antidepressant treatment by patients on chronic hemodialysis and their family caregivers [115]. This study suggests that patients may refuse recommendations for antidepressant therapy due to attributing their depression to an acute event, chronic illness or their dialysis therapy. Patient lack of interest in antidepressant medication was demonstrated by the high dropout rates in the study by Wuerth and colleagues, where only 45% of eligible patients agreed to receive the intervention after being assessed for depression [116]. Although the reasons for patient reluctance to accept pharmacological therapies were unclear, it is suspected this may be due to the already high medication burden among ESKD patients. A study by Johnson and Dwyer [117] reported that 50% of patients on dialysis who had elevated BDI scores were not aware of their depressed symptoms or did not believe that they needed help and believed they could improve without intervention or support. One study found that patients believed their depressed symptoms to be an inevitable part of their illness experience [25]. A sense of hopelessness is symptomatic of depression and could also prevent patients with depression from seeking help or seeing any benefit from psychological intervention.

Various studies provide insight into the relevance and importance of depression to patients and their family caregivers. A study published in 2014 conducted a national survey of Canadian adult patients who were on dialysis or about to commence dialysis, as well as their caregivers and health professionals [118]. As part of this study, a workshop was held to determine the top 10 research questions. This study identified depression as one of the top priorities among participants. Qualitative studies across all stages of kidney disease have identified psychosocial outcomes of living with kidney disease to be important and particularly relevant to the lived experience of patients with kidney disease and their family caregivers [14]. The standardized outcome in nephrology initiative (SONG) has been working to identify the most important outcomes across different

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patient subgroups to develop a set of core outcomes to improve the relevance and consistency of outcomes reported in randomized controlled trials in nephrology [112]. Patients and caregivers contribute to this process. Psychosocial outcomes have not been ranked highly when compared to the medical outcomes, and outcomes like depression and anxiety have been ranked lower primarily because participants believe that these outcomes are easily treatable or within their personal control.

Many units do not have available resources, including psychologists, to provide time-intensive psychological interventions, which would need to be available to different cultures and patients of multiple languages. There is also difficulty in providing face-to-face CBT programs to patients around dialysis schedules, and patients are unwilling to travel to the hospital on nondialysis days given their already highly demanding and interfering treatment requirements [25, 119]. Recent studies have aimed at increasing accessibility of psychological interventions by providing chair-side treatment [94] or using e-health technology [96, 120].

A stepped-care model has also been proposed for the management of depression in the dialysis context [120]. Within this model, patients with mild-moderate symptoms (e.g. PHQ-9 scores between 5 and 19) would be referred for self-help interventions. Patients with suicidal ideation or moderate to severe depression and/or anxiety (i.e. PHQ-9 score of 20–27) would be referred to liaison psychiatry or a renal clinical psychologist, whereas those with severe depression and suicidal ideation (PHQ-9 score 20–27) would be referred more urgently for psychological interventions.

Conclusions

Depression appears to be common among patients with CKD and ESKD, and a range of biological, demographic, psychosocial, and cognitive factors increase the risk of depression. Depression has been associated with adverse outcomes including increased rates of mortality, suicide, treatment withdrawal, hospitalization, nonadherence, infection, and impaired QoL. Nevertheless, depression is underdetected and undertreated in this population. There is limited evidence for the treatment of depression in patients with CKD and ESKD, and there are patient, family caregiver, healthcare provider, and service delivery barriers to the assessment and treatment that need to be addressed. Most of the research on the epidemiology and treatment of comorbid depression in this population has been conducted in adults on hemodialysis. Large-scale randomized controlled trials are needed to inform treatment for all patients across the trajectory from CKD to ESKD, different treatment modalities, and age groups, including pediatric patients.

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Pain

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Introduction

Pain is a common and distressing symptom that affects patients with chronic kidney disease (CKD) throughout their illness. Pain is inadequately treated for many patients with advanced CKD [1, 2] and there is tremendous variability within and between countries in the management of pain, including the prescribing patterns of analgesics [3]. The International Association for the Study of Pain defines pain as "An unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage" [4]. This definition reflects the complex and multidimensional phenomenon of pain with physical, psychosocial, and spiritual components. The recognition of this complexity represents "a major advance over an exclusively sensory focus on pain" [5]. Its importance for clinicians, including nephrologists, is clear: that the assessment and management of pain requires a broad perspective.

This chapter reviews the epidemiology of pain reported worldwide for patients with CKD, including its impact on patient outcomes, and outlines strategies for the clinical assessment and management of acute and chronic pain. This will include both nonpharmacologic and pharmacologic interventions, and the role analgesics play in the overall approach to pain management.

Epidemiology

The high prevalence and severity of pain reported by dialysis patients has been well documented. Thirty-five studies examining the prevalence and severity of pain in 7832 hemodialysis patients from 20 countries have been published since 2000 [6–40]. Nineteen of these studies looked at overall pain: the pooled mean prevalence was 68.9% (95% confidence interval [CI] 67.7–70.2) and the prevalence of moderate or severe pain was 40.4% (95% CI 38.9–41.9) [9, 11, 16, 18–22, 24–27, 30, 31, 35–38, 40]. Fifteen of these studies focused on either bone/joint pain or muscle pain. These pains were also common, with mean prevalence rates of 46.4% (95% CI 43.5–49.2) and 59.4% (95% CI 57.6–61.7), respectively. When prevalence rates were restricted to those experiencing moderate or severe pain, 26.7% reported moderate or severe bone/joint pain and 31.3% reported moderate or severe muscle pain. Pain prevalence remained high in patients following withdrawal from dialysis (54.6%) [41, 42], even in the last 24 hours of life (36.0%) [41, 42].

Pain prevalence data for patients receiving peritoneal dialysis are much more limited. While seven studies from five different countries included data on peritoneal dialysis patients [6–8, 15, 16, 28, 38], only one reported their hemodialysis and peritoneal dialysis data separately [28]. For those 573 peritoneal dialysis patients, the prevalence of muscle pain was 64%.

Only five studies have explored pain in conservative kidney management (CKM), i.e. glomerular filtration rate (GFR) category five (G5) patients who had chosen conservative, nondialysis care [38, 43–46]. These were all small studies with a total of 271 patients from four countries: Republic of Guinea, United Kingdom, Australia, and China. Pain was experienced by 66.8% of patients at the time of initial assessment and increased to 73.4% in the last month of life. However, only 26.1% of these patients reported their pain as moderate or severe in intensity.

Data are limited for the prevalence of pain in patients with earlier stages of CKD, prior to the need for dialysis. Five studies from four countries have presented data on 2170 predialysis patients with various stages of CKD [6,

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47–50]. The prevalence of overall chronic pain of 67.1% in G1-2 CKD patients appears similar to the 62.3% reported for G3-5 CKD patients. In one small study there were no statistically or clinically significant differences in mean pain severity scores between CKD stages, which ranged 4.8/10 to 5.7/10 for the entire population and 6.9–7.6/10 when calculated for those reporting pain [49].

There is great variation and often a lack of detail around the type and chronicity of pain in studies reporting on pain, which has tremendous implications on the impact of patient outcomes and the appropriate treatment strategies. While most studies attempt to describe chronic pain, the definitions of chronic pain included "pain experienced outside of dialysis sessions" and various durations of pain that included 7 days, 2 weeks, 4 weeks, 6 weeks, 3 months and "lasting weeks, months or even years." Studies rarely differentiated nociceptive from neuropathic pain. Despite these limitations, it is clear that the prevalence of pain is very high for patients with advanced CKD.

Clinical Relevance of Experiencing Pain

The impact of pain varies enormously between individuals, but those living with pain, specifically chronic pain, generally suffer from other physical and psychological consequences. A recent systematic review showed that people living with chronic pain experience depressive thoughts, disability, lower quality of life (QoL), conflicts in close relationships, and reduced participation in many social aspects of everyday life [51]. For patients with CKD, chronic pain has the same pervasive and detrimental effects on their lives and is associated with psychological distress, depressive disorders, limitations in work, family, and social life, and decreased life satisfaction and QoL [1, 16, 52–54]. For hemodialysis patients, severe pain has been shown to be independently associated with shortened or missed hemodialysis treatments (IRR 1.16, 95% CI 1.06–1.28) and increased health services utilization such as emergency departments visits (IRR 1.58, 95% CI 1.28–1.94) and hospitalizations (IRR 1.22, 95% CI 1.03–1.45) [36]. Chronic pain in the United States costs hundreds of billions of dollars annually [55]. When caring for people with chronic pain, it is essential that interventions and their evaluation take into consideration these far-reaching consequences.

Key Considerations in the Assessment of Pain

Routine screening for pain in patients with CKD is important for several reasons. First, pain is common in patients with CKD, as evidenced by the epidemiological data above. Second, a dance of silence may occur whereby patients do not volunteer they have pain and physicians do not enquire. Clinicians can only discern the pain experience of a patient by enquiring or, in the case of cognitive impairment, observing and asking carers. Third, it is important to treat acute pain in a timely fashion before it becomes chronic and, through pathological neuronal changes, a disease in its own right [56]. Moving from unawareness to awareness of the presence of pain hopefully triggers a response in management that may include a multidisciplinary approach including clinicians with pain expertise given that the evaluation of pain requires a comprehensive patient assessment and physical examination.

Four key aspects of the patient's assessment essential to determining a comprehensive approach to pain management include determining (i) pain intensity, (ii) chronicity and possible reversible causes for the pain, (iii) the type of pain (nociceptive, neuropathic or combined), and (iv) treatment goals.

Determining pain intensity helps establish the need for treatment. Pain is always subjective and unique to each individual. As such it can only be measured by that individual. Culture, ethnicity, mood, and the perceived meaning of the pain may influence how a patient experiences and reports pain. The concept of "total pain" refers to the physical, psychological, social, and spiritual influence on a patient's perception of pain. Listening to the patient validates the significance of their pain and their suffering, and is an important part of the therapeutic intervention. Pain that is perceived by the patient as mild, e.g. reported as a score of 1–3/10, does not usually require initiation of or a change in pain management. Pain perceived as moderate, e.g. reported as a score of 4–6/10, generally means therapy has to be initiated or changed as pain management is inadequate. Pain described as severe or rated as 7–10/10 typically requires immediate attention to treatment. Regularly enquiring about and recording the severity of pain is critical in following the progress of management. Clinicians should be aware that the assessment of pain in patients with cognitive impairment is focused on behavioral changes, such as crying out, facial grimacing, and protecting certain parts of the body.

Determining the chronicity of pain is important in understanding the potential long-term implications for the patient and in determining appropriate management strategies (Table 74.1). Acute pain is generally due to tissue injury: it is important to treat underlying causes to ensure long-term resolution. Although we still do not fully understand the development of chronic pain, lessons learned from patients undergoing surgery have taught us that good acute pain control reduces the likelihood of experiencing chronic pain. Chronic pain is much more

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Table 74.1 Defining the chronicity of pain.

Acute pain	
Pain characteristics	Typically persists for less than 3 months Associated with tissue damage Usually episodic with periods without pain
Clinical implications	• Tends to last a predictable period, have no progressive pattern, and subsides as healing occurs • Tends to respond well to pharmacologic therapy: titrating analgesics against pain intensity usually works well
Chronic pain	
Pain characteristics	• Often defined as any painful condition that persists for more than 3 months [4] • Usually initiated by tissue injury but is perpetuated by neurophysiological changes which take place within the peripheral and central nervous system leading to continuation of pain once healing has occurred • Severity is often out of proportion with the extent of the originating injury
Clinical implications	• More likely to result in functional impairment and disability, psychological distress, sleep deprivation, and poor quality of life than acute pain • The pain experience may be impacted substantially by mood, stress, and social circumstances • May not respond well to analgesics, including opioids, except early in the course of treatment.

likely to result in poor patient outcomes such as functional impairment, psychosocial distress, and poor QoL. As the disorder of chronic pain progresses, the original triggers become less important and the psychological mechanisms gain importance. As a result, patients with chronic pain often do not have a clear treatable underlying cause for their pain. Pharmacologic therapy alone is unlikely to be sufficient and nonpharmacologic assessment and support are essential.

Recurrent pain should be distinguished from chronic pain: it is pain from recurrent tissue injury, which may occur over long periods of time. Examples include pain from needling fistulas, intradialytic steal syndrome, and intradialytic headaches and cramps. The management of recurrent pain is more in keeping with acute pain: it focuses on strategies to minimize tissue injury and short-term pharmacologic management around the time of tissue injury if the cause cannot be avoided. Although recurrent pain typically has no progressive pattern and patients will be free from pain for long periods of time, it tends to be more intrusive on everyday life than acute pain.

Table 74.2 Distinguishing between nociceptive and neuropathic pain

Nociceptive pain	
Pain characteristics	Results from tissue damage in the skin, muscle, and other tissues, causing stimulation of sensory receptors May be described as sharp or like a knife and often felt at the site of damage With stimulation of visceral nociceptors, may be experienced as a dull, aching, and poorly localized
Clinical implications	Tends to respond to analgesics
Neuropathic pain	
Pain characteristics	Results from damage to the nervous system resulting in either dysfunction or pathological change May be felt at a site distant from its cause, e.g. in the distribution of a nerve Common descriptors include burning, shooting, and electrical May be associated with episodes of spontaneous pain, hyperalgesia, and allodynia; the presence of allodynia is pathognomonic
Clinical implications	Responds poorly to analgesics and typically requires adjuvant therapy

The choice of initial analgesic treatment is dependent upon whether the pain is neuropathic or nociceptive in nature (Table 74.2). Nociceptive pain is caused by damage to body tissue and responds well to nonopioid and opioid analgesics, at least in the short term. In contrast, neuropathic pain results from abnormal stimulation of sensory receptors due to nerve damage and is poorly responsive to nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids or requires doses for response that are associated with unacceptable toxicity. The initial treatment of neuropathic pain is an adjuvant drug, which is a drug that has a primary indication other than pain. Many pains experienced by patients with CKD will be of mixed type, e.g. pain associated with ischemia and calciphylaxis. It is important to target the neuropathic component first with adjuvant therapy to prevent inappropriate use of opioids.

Developing a treatment plan includes explaining the nature of the pain condition and setting appropriate treatment goals. Since relief of all pain is generally not possible, especially with chronic pain, the goal of therapy is to relive the pain to a tolerable level, allowing for acceptable function and QoL. For most patients this is a target of ≤3/10. The functional goals that patient sets, such as the ability to ambulate, sleep or interact socially, will need to be incorporated into the follow-up assessment of the patient.

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Pain Assessment Instruments

In terms of pain assessment instruments, there are two broad approaches (Table 74.3):

1) Generic pain assessment instruments used across all conditions.
2) Validated kidney-specific symptom assessment instruments that include pain.

Each of the kidney-specific symptom instruments are global symptom assessment tools that include pain as one of many symptoms recorded. The most widely used are the Integrated Palliative care Outcome Scale I-POS (Renal) and the Edmonton System Assessment System – revised: Renal (ESAS-r:R). The I-POS (Renal) asks the patient to record the severity of pain in the past week on a 5-point Likert scale of severity that ranges from nil to overwhelming [57]. The ESAS-r:R asks the patient to record the severity of pain on visual analogue and numerical rating scales from 0 to 10 [52, 58]. The recall period can be current pain or pain in the past week.

Using the above tools to determine pain intensity alone is insufficient beyond initial screening. Elucidating the other core components of the pain assessment (chronicity and type of pain) can be done through the "PQRST" approach: **P**rovokes and Palliates, **Q**uality, **R**egion and **R**adiation, **S**everity, and **T**ime, as outlined in Table 74.4 [59]. Other core domains that should be assessed when managing pain include physical and psychosocial function, QoL, and adverse events. These are incorporated into the multidimensional pain assessment instruments as outlined in Table 74.3.

Table 74.3 Generic pain assessment instruments and kidney-specific global symptom assessment instruments that include the symptom of pain.

Generic pain assessment instruments

Severity scales

1) Visual analogue scale (VAS). Self-reported rating of pain from zero ("no pain") to 10 ("the worse pain imaginable") on a 10 cm line.
2) Categorical numerical scale. Ask patient to report pain severity from 0 to 10.
3) Categorical verbal rating scales. Rating pain as none, mild, moderate, or severe.

PEG scale: Assesses pain and its effect on the function and enjoyment of life of the patient.

Abbey scale: An instrument designed and validated for the assessment of pain in people with significant cognitive impairment.

Physical symptom distress scale (PSDS): Assesses 16 symptoms, including pain.

Brief Pain Inventory (BPI): Assesses location, type (nociceptive v neuropathic) and severity of pain.

Short Form McGill Pain Questionnaire (SF-MPQ): Self-reported pain severity. Does not assess the effect of pain on function or QoL

Kidney-specific symptom assessment instruments that include pain

I-POS (Renal): Combination of 17 symptoms, including pain, plus a series of psychosocial questions.

Palliative care Outcome Scale *POS-renal*: The precursor to the I-POS (Renal). Seventeen symptoms, including pain.

Dialysis Symptom Index (DSI): Assesses 30 symptoms, including pain. Validated for dialysis patients only.

ESAS-r: Renal: Eleven visual analogue scales with a superimposed 0–10 scale for 10 symptoms, including pain and wellbeing.

*Kidney Dialysis Quality of Life – Short Form/SF-36 (*KDQOL-SF*)*: Self-reported QoL measure for CKD patients.

*Choice Heath Experience Questionnaire (*CHEQ*) and SF-36*

Nonpharmacological Approach to Pain Management

A vital component of the management regimen of chronic pain is the use of nonpharmacological therapies. This aspect of comprehensive pain care has a prominent place in all evidence-based guidelines on pain management, especially chronic nonmalignant pain. A recent guideline promulgated by the United States Center for Disease Control recommends nonpharmacological treatment of chronic nonmalignant pain [61]. The recent Clinical Practice Guideline from the American College of Physicians recommends that nonpharmacological interventions should be the first-line management of chronic low back pain [62]. Indeed, in the modern era there is a strong focus on a multimodal and multidisciplinary approach to chronic pain management [63]. The evidence for these and other therapies is described below. Unfortunately, there is a significant dearth of nonpharmacological intervention studies on patients with CKD.

Physical Therapies

Exercise

A systematic review of guidelines for the physical management of osteoarthritis found the level of evidence for exercise ranged from low to high and the overall recommendation was strong [64]. Two subsequent authoritative guidelines reached the same conclusion [61, 63]. The effect of general exercise, aerobic exercise, and resistance training has been well studied, especially for osteoarthritis of the knees [65]. The findings of these studies were mostly positive, although some found no effect. The quality of these studies was low to moderate [65]. For chronic

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Table 74.4 The PQRST approach to evaluating pain [59]

Components of the assessment	Questions to explore
P = Provokes and Palliates	What causes the pain? What makes the pain better or worse?
Q = Quality	What does the pain feel like? Is it sharp? Dull? Stabbing? Burning? Crushing?
R = Region and Radiation	Where is the pain located? Is it confined to one place? Does the pain radiate? If so, where to?
S = Severity	How severe is the pain?
T = Time (or Temporal)	When did the pain start? Is it present all the time? Are you pain-free at night or during the day? Are you pain-free on movement?

Adapted from Davison [60] with permission.

lower back pain, moderate quality evidence showed that exercise resulted in a small improvement in pain and function [66]. A recent meta-analysis found that both aerobic training and progressive resistance training reduced the severity of chronic low back pain significantly, with neither mode being superior to the other [67].

Weight Reduction

Weight reduction is strongly recommended across all guidelines for osteoarthritis pain of the knees [64, 65]. In studies that vary from very low to moderate quality, the effects of weight reduction varied from no effect to a positive effect [65].

Yoga

In one of the few intervention studies for pain in CKD patients, a yoga-based exercise program reduced pain in hemodialysis patients in a randomized controlled trial by 37% [68]. The American College of Physicians Guideline on chronic low back pain recommends yoga, albeit with low-quality evidence [62].

Acupuncture

A large individual patient meta-analysis showed good evidence for the efficacy of acupuncture in chronic musculoskeletal pain [69] and the systematic review of guidelines on the management of osteoarthritis recommended this treatment [64]. Similar results were found in meta-analyses of pain management in diabetic peripheral neuropathy and carpal tunnel syndrome, although in each case caution was expressed about the quality of the methodology in the randomized controlled trials (RCTs) examined [70]. Indeed, a recent Cochrane Review on the role of acupuncture in neuropathic pain concluded that there was insufficient evidence to support or refute its use [71].

Miscellaneous

There is low-quality evidence on the effect of thermal therapy, whole-body vibration, massage, and tai chi on chronic pain. Nevertheless, the systematic review of guidelines on the management of osteoarthritis recommended thermal therapy [64]. Given the increasing proportion of patients with CKD secondary to diabetic nephropathy, there are two physical treatments that should be noted. First, high-tone external muscle stimulation showed a statistically significant efficacy in a prospective pilot study in dialysis patients with symptomatic diabetic and uremic neuropathy [72]. Second, the role of mirror therapy for phantom limb pain following amputation was assessed in two recent systematic reviews and it was found that this intervention, while successful, was based on studies that were of low to moderate quality [73, 74].

Behavioral therapies

Education

Education and self-management are core recommendations in all major guidelines for chronic noncancer pain generally and for specific pain syndromes such as osteoarthritis [64]. Reviews of their role showed a spectrum from positive to no effects [65].

Psychological Intervention

Overall, reviews on the studies of the effect of cognitive-behavioral therapy (CBT), mindfulness-based interventions, and stress-management training on chronic pain have been positive [65]. The studies were of very low to moderate quality. In a systematic review of 42 RCTs for patients with chronic noncancer pain except headache, CBT was found to have a small to moderate effect on pain [75].

Interventional

The American Society of Interventional Pain Physicians, in their recent guidelines on chronic noncancer pain, stated that "multiple interventional techniques have been described in managing chronic pain with discordant opinions, often based on inappropriate evidence synthesis leading to inappropriate and often negative conclusions" [63]. They concluded that the level of evidence across numerous systematic reviews on interventional techniques was "at least moderate" [63]. They found

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significant effectiveness for epidural injections for spinal pain, with a wider range of evidence for facet or zygapophysial joint injections [63].

Pharmacologic Approach to Pain Management

Analgesics play an important role in pain management. However, for patients with chronic pain, where the somatosensory component of the pain tends to be more important than the original tissue injury, pharmacologic treatment should only be used to augment the previously discussed nonpharmacologic therapies as required to meet patient-specific treatment goals. Unfortunately, data remain sparse even in the general population for the benefit of analgesics in managing chronic pain. While there is some moderate and low-quality evidence suggesting that long-term treatment with opioids can lead to significant improvements in functional outcomes and QoL in patients with chronic, nonmalignant pain, findings are not conclusive [76].

Current Analgesic Use in CKD

In recent years there has been an escalation in the prescribing and dose of opioids, resulting in an increase in opioid-related deaths, higher rates of addiction and social dysfunction, cognitive impairment, falls and orthopedic injuries in the elderly, and an increase in emergency department visits and in-patient hospitalizations [77, 78]. The rates of harm correlate directly with dose and continuous use. There is growing concern at regulatory, professional, and societal levels about opioid misuse, with the greatest focus being on high dosing and chronic use. Those most at risk for these adverse effects are adults aged 18–25 years, men, those with lower educational attainment, and people with psychiatric conditions or a history of substance or sexual abuse [77, 78].

The prevalence of overall analgesic and opioid use in CKD is highly variable within and between countries, and the differences cannot be accounted for by patient characteristics. A meta-analysis reported an estimated prevalence of overall analgesic use in patients with G4 and G5 CKD of 47% (95% CI 0.35–0.59), opioid prevalence 22% (95% CI 0.07–0.41), acetaminophen prevalence 26% (95% CI 0.16–0.36), and NSAID prevalence 16% (95% CI 0.11–0.21) [3]. The prevalence of opioid use is much higher in the United States compared to Europe, Canada, Australia, and New Zealand [3]. A large study across the United States showed that 64% of over 150 000 dialysis patients received opioids in 2010: 41% of patients had a short-term prescription while 23% received a chronic opioid prescription defined as ≥90 days [79]. Equally concerning was the choice of opioid used: 46% of these patients, representing 10.6% of entire hemodialysis cohort, received chronic prescriptions for opioids that are not recommended, while almost all other patients were prescribed hydrocodone, an opioid for which there is no evidence for its safety in patients with CKD. Only 1.9% of patients received a chronic prescription for an opioid that is recommended for use in the context of advanced CKD. The current high use of opioids for patients on hemodialysis in the United States is associated with a higher risk of altered mental status, falls, and fractures in a dose dependent manner [80].

Screening for High Risk of Opioid Misuse

Maintaining a balance between the legitimate needs of patients in pain and minimizing the risks of drug-aberrant behavior and addiction has proven challenging. First, it is important to distinguish tolerance and physical dependence, which are known effects of opioids, from compulsive opioid seeking and addiction (see Table 74.5). Recent comprehensive, evidence-based guidelines on the use of opioids in the management of chronic, nonmalignant pain [61, 63, 81] recommended several steps in this process:

1) First, determine carefully whether opioids are appropriate for the pain syndrome being addressed.
2) Second, if opioids are being considered, conduct an assessment of risk factors for substance use disorder. There is no single test or instrument that absolutely predicts this risk. Indeed, the United States Center for Disease Control and the American Society of Interventional Pain Physicians found the level of evidence for the reliability of these instruments to be "insufficient" and "limited" [61, 63]. Nevertheless, and conscious of these limitations, all bodies enumerated a series of risk factors to be considered by clinicians, which are shown in Table 74.6.
   The next steps are counsels of caution. They include the following when prescribing opioids:
   (a) Use, where available, a prescription monitoring program, which tracts in real time the history of prescriptions to detect a patient seeking multiple prescriptions from different physicians.
   (b) consider drawing up an opioid contract with the patient setting clear goals to the management, including the level of analgesia and restoration of function acceptable to the patient.
   (c) advise the patient to employ universal precautions, including a clear statement on the risks and benefits of opioid therapy, commencing with a trial of opioid therapy, regular reviewing, and emphasizing the security of medications at home.

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(d) For patients deemed at high risk of substance use disorder, consider opioid therapy "only if they are able to implement more frequent and stringent monitoring parameters" and in consultation with a mental health or addiction specialists [81].

The Essential Principles

The essential principles of prescribing analgesics for pain management are summarized by five phrases that are described within the context of advanced CKD in Table 74.7.

Table 74.5 Defining drug tolerance, physical dependence, and addiction.

Tolerance

- Tolerance is defined as the need for increasing doses of a drug to achieve the same pharmacological action.
- It can occur to unwanted effects such as respiratory depression and nausea as well as to the desired pain relief.
- Although considered an expected response to chronic opioid use, the incidence is unclear. Studies of patients with malignant chronic pain show that after a period of dose titration patients may continue on the same dose of morphine for many months without needing to increase the dose and that the requirement for dose escalation is usually on account of progression of disease.

Physical dependence

- Physical dependence is characterized by withdrawal symptoms if treatment is stopped abruptly or if an antagonist is given. If pain is relieved by other means, e.g. abrupt pain reduction following a nerve block, the dose will need to be reduced to prevent respiratory depression, but low as needed doses may be required initially to treat withdrawal symptoms.

Addiction

- Addiction is a behavioral pattern characterized by loss of control over use, compulsion to use, craving, and continued use of a drug despite knowledge of harmful consequences.

Table 74.6 Risk factors for substance use disorder.

1) Current or past illicit drug or alcohol abuse.
2) Family history of alcohol or drug abuse.
3) History of sexual abuse, psychiatric disorder or post-traumatic stress disorder.

Source: Based on guidelines on opioid use in chronic nonmalignant pain published by the American Pain Society – American Academy of Pain Medicine (APS-AAPM), the Center for Disease Control (CDC), American Society for Interventional Pain Physicians (ASIPP), British Pain Society (BPS), Canadian National Opioid Use Guideline Group (NOUGG) and Australian and New Zealand College of Anaesthesiology (ANZCA).

The World Health Organization advocates a cautious stepwise approach to analgesic therapy for malignant and nonmalignant acute and chronic pain [83]. It involves the slow introduction and upward titration of analgesics, starting with nonopioids then progressing to weak then strong opioids as required for pain relief. There is preliminary evidence only to suggest that this approach may be appropriate and effective in hemodialysis patients with mild or moderate nociceptive and neuropathic pain [84]. Of particular importance is the careful selection of analgesics. Current recommendations are based on indirect pharmacologic evidence and clinical experience, i.e. "expert advice," rather than high-quality clinical studies: data remain scare. In view of the potential for toxicity and the narrow therapeutic window in patients with advanced CKD, short-acting rather than long-acting preparations should be used until stable pain relief has been achieved. There is also some evidence for increased mortality with long-acting opioids [82].

Adverse effects of strong opioids are sufficiently common to prevent effective analgesia, and patients should be warned of these and informed of the steps that can be taken to prevent or treat them at the time of opioid initiation. Constipation is nearly universal and persistent so patients should have a bowel routine, e.g. Polyethylene Glycol 3350 prescribed preemptively. Nausea and vomiting occur in about 50% of people, wearing off in most after 7–10 days. Central nervous system effects occur most frequently on initiating strong opioids and when increasing the dose, hence the need to "start low and titrate slow." Respiratory depression is unusual if oral, short-acting preparations are used and the dose is titrated slowly against pain and toxicity. When pain is stable, strong opioids can be used in long-acting preparations such as transdermal fentanyl or methadone. Hallucinations are a very distressing adverse effect of opioids and if they occur should be managed by dose reduction, switching to an alternative opioid, or with coadministration of haloperidol. The Center for Disease Control recommends that physicians mitigate risk of toxicity by offering naloxone when factors that increase risk for opioid overdose are present. These include a history of overdose, history of substance use disorder, higher opioid dosages (≥ 50 morphine milligram equivalents/day), or concurrent benzodiazepine use [61].

The Selection of Analgesics for Patients with Advanced CKD

Many analgesics and their metabolites are excreted by the kidneys. The analgesics that should be avoided in patients with advanced CKD and the evidence behind the

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Table 74.7 The five principles of pain management within the context of advanced CKD.

Principle	Description	Specific considerations in advanced CKD
By mouth	Oral administration is safest and therefore usually preferred If ingestion or absorption is uncertain, analgesics need to be given by alternative routes such transdermal, rectal or subcutaneous	HD patients have easy intravenous access, but this is to be avoided as the route of administration for analgesics to optimize safety and minimize the risk of abuse and addiction
By the clock	For continuous or predictable pain, analgesics should be given regularly. Additional "breakthrough" or "rescue" medication should be available on an "as needed" basis in addition to the regular dose.	Some patients with mild-moderate pain may achieve adequate pain relief with analgesic dosing post-HD only. An example would be mild-moderate neuropathic pain dosed with gabapentin post-dialysis.
By the ladder	Pharmacologic management proceeds stepwise from nonopioids to low-dose opioids The drug should be used at its full tolerated dose before moving to the next level	Careful selection of analgesics based on severity of kidney failure with gradual titration is essential Sustained-release preparations are generally not recommended, at least until the individual patient's response to the medication has been observed, due to the narrow therapeutic window in patients with advanced CKD There is some evidence for increased mortality with long-acting opioids [82]
For the individual	The "correct" dose for strong opioids is the amount needed to relieve the pain without producing intolerable side effects. Evaluation of benefit and toxicity is essential. If an individual finds that a particular strong opioid causes unacceptable adverse effects, an alternative must be sought	Chronic pain is often experienced in the context of numerous other physical, psychosocial, and spiritual concerns, including end-of-life issues. Close attention to these other issues must not be forgotten if the pain management strategy is to be successful.
Attention to detail	Pain changes over time, therefore there is the need for ongoing reassessment Side effects of opioids should be explained and managed actively, e.g. constipation and nausea, with anticipatory prescribing of a bowel routine, e.g. PEG 3350 and antiemetic, e.g. Zofran 4–8 mg Offer naloxone when factors that increase risk for opioid overdose or concurrent benzodiazepine use are present	There are no studies on the long-term use of analgesics in patients with CKD. Careful attention must be paid to efficacy and safety. The impact on overall symptom burden, physical function, emotional state, cognition, and quality of life should be assessed routinely

CKD, chronic kidney disease; HD, hemodialysis. Adapted from Davison [60] with permission.

recommendations have been recently reviewed and are outlined in Table 74.8 [60].

Nonopioids for Patients with Advanced CKD

Acetaminophen

Acetaminophen is the initial analgesic of choice for patients with advanced CKD. Acetaminophen is an antipyretic analgesic with weak anti-inflammatory activity and is metabolized extensively in the liver. Only 2–5% of the dose is excreted unchanged in the urine and there are no clinically significant changes observed in patients with advanced CKD. Recent evidence suggests that lifetime cumulative doses of acetaminophen do not have an adverse effect on CKD progression [99]. The recommended maximum daily dose is 3000 mg given that liver injury can be seen with doses of <4000 mg.

Nonsteroidal Anti-Inflammatory Drugs

Geriatric and rheumatologic societies recommend that the chronic (>21 days) use of all oral NSAIDs, including high dose aspirin, be avoided, especially in the elderly (≥75 years) [85]. Clinicians should be particularly cautious about their use in patients with CKD due to increased risks of bleeding, cardiovascular events, psychiatric events, and kidney-related complications in those with residual kidney function (Table 74.8). NSAIDs are there-

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Table 74.8 Analgesics to avoid in patients with advanced CKD.

NSAIDS (for chronic pain) [85]

- The major limitation is GI toxicity due to inhibition of cytoprotective mucus secretion and impaired platelet aggregation resulting in ulceration and bleeding. Risk increases in severity and frequency with increasing age: NSAID use increases the risk of GI bleeding in the elderly fourfold. Concomitant use of antiplatelet drugs such as aspirin, anticoagulants, and SSRIs further increases bleeding risk.
- Although the GI safety profile of COX-2 inhibitors is superior to nonselective NSAIDs, nephrotoxic and cardiovascular adverse effects (myocardial infarction, thrombotic events, and stroke) remain significant. It has been shown that the long-term use of all NSAIDs increases the risk of stroke by 64% at 2 years. COX-2 selectivity may not play a role in the increased cardiovascular risk of NSAIDs as Rofecoxib was the only drug in meta-analyses to demonstrate excessive harm and skewed the data of COX-2 selective NSAIDs [86]. There is insufficient evidence to confirm any NSAID to be safe in terms of cardiovascular risk.
- In patients with residual kidney function, NSAIDs may also cause a reduction in GFR that can be severe and irreversible if the patient has decreased effective circulating volume, sodium and water retention, which may aggravate hypertension, and hyperkalemia.
- The elderly may also be at increased risk for NSAID-associated psychiatric events such as agitation, depression, anxiety, paranoia, delirium, and hallucinations.

Codeine

- A weak opioid that is metabolized by the enzyme CYP2D6 in the liver to its active metabolite morphine, which provides the analgesic effect. Only about 5–10% of codeine is metabolized in this pathway, with most of the administered dose being converted to inactive metabolites.
- The percentage of codeine converted to morphine can be much higher in individuals who have three or more active copies of the *CYP2D6* gene (ultra-rapid metabolizers), resulting in life-threatening or fatal respiratory depression due to high plasma levels of morphine, even with trivial doses. Conversely, poor analgesic response will be seen in those who carry inactive copies of *CYP2D6* (poor metabolizers) due to low morphine levels after administration of standard doses [87].
- Up to 11% of codeine is also metabolized to hydrocodone (mechanism unknown).
- Both codeine and its metabolites are excreted by the kidneys and accumulate in patients with kidney failure.

Dextropropoxyphene

- A weak opioid that has been withdrawn from the market in the United Kingdom, Europe, New Zealand, and Canada due to its weak analgesic effect, addictiveness, and its association with deaths and possible arrhythmias. In the United States it has a Black Box warning and is on the High Risk Medications in the Elderly list.
- Decreased elimination of dextropropoxyphene and its major active metabolite, norpropoxyphene, occurs in patients with kidney failure [88].

Tramadol

- A weak synthetic opioid, related to codeine.
- Extensively metabolized in the liver with one main active metabolite, O-desmethyltramadol (M1). Both the parent drug and M1 contribute to the analgesic effect through u-opioid receptors and two nonopioid mechanisms, inhibition of serotonin, and norepinephrine reuptake [89]. M1 has a significantly higher affinity for opioid receptors than tramadol, while tramadol is a more potent inhibitor of serotonin and norepinephrine reuptake [90].
- The enzyme CYP2D6 catalyzes the production of M1 and other CYP enzymes (CYP2B6 and CYP3A4) catalyze the production of M2, an inactive metabolite (Figure 74.1).
- Unpredictable risk of serious overdosing or underdosing after administration of standard doses. The concentrations of tramadol may be 20% higher in "poor metabolizers" versus individuals who have multiple functional copies of the CYP2D6 gene ("ultrarapid metabolizers"), while M1 concentrations may be up to 40% lower. Factors such as the concurrent use of CYP2D6 inhibitors (Figure 74.2) could also result in increased tramadol concentration and decreased M1 concentration.
- Induction of CYP3A4 may pose an added risk of seizures, even when tramadol is administered in accepted doses. This is particularly problematic in the context of neuropathic pain where several of the adjuvants are CYP3A4 inducers (Figure 74.2).
- Serotonin syndrome is a potentially life-threatening syndrome that may occur with the use of tramadol, especially if other medications such as antidepressants or other drugs that impair the metabolism of tramadol (CYP2D6 and CYP3A4 inhibitors) are used concurrently. Symptoms include changes in mental status (e.g. agitation, hallucinations, coma), autonomic instability (e.g. tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g. hyperreflexia, incoordination), and/or GI symptoms (e.g. nausea, vomiting, diarrhea).

(*Continued*)

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Table 74.8 (Continued)

Morphine

- Metabolized primarily to the active metabolites morphine-3-glucuronide (M3G) and small amounts (~10%) of morphine-6-glucuronide (M6G). M3G lacks analgesic effect but may have neuroexcitatory effects contributing to adverse effects such as allodynia, myoclonus, and seizures. M6G has potent analgesic effect, more so than morphine. Although M6G is dialyzed, it diffuses out of the central nervous system slowly so may not be completely removed during dialysis.
- M3G and M6G (more so than the parent drug morphine) accumulate in patients with advanced CKD.
- There is poor, inconsistent correlation between plasma levels of morphine, M3G, and M6G, and clinical efficacy or adverse effects [91]. The best correlation appears to be between higher levels of morphine and constipation and high levels of M3G and cognitive impairment [92]. There are many reports in the literature of profound toxicity in patients with advanced CKD.

Oxycodone

- A semisynthetic opioid metabolized primarily by CYP3A4 to the active metabolite noroxyodone with a small amount metabolized by CYP2D6 to the active metabolite oxymorphone, the clinical relevance of which is not clear. The potential for drug interaction and unpredictable pharmacodynamic response therefore is relatively high (Figure 74.1).
- Less than 10% is excreted unchanged in the urine. Despite this, both the parent drug and the active metabolites appear to accumulate in dialysis patients [93] with reports of toxicity [94]. The central opioid effects are governed by the parent drug.
- A recent systematic review of opioid use in cancer patients with some degree of kidney failure found two studies that evaluated oxycodone use: higher oxycodone levels were associated with increased fatigue but the metabolite noroxycodone was not associated with any of the evaluated adverse effects [92].
- A single study assessed the pharmacokinetics following a single 20 mg oral dose of an abuse-deterrent formulation of extended-release oxycodone in patients with mild ($n = 6$), moderate ($n = 5$) or severe ($n = 6$) kidney failure [95]. C_{max} and AUC continued to increase with increasing severity of kidney failure and patients with severe kidney failure had a C_{max} (31.6 ng/ml vs. 17.6 ng/ml) and AUC (493.5 ng.h/ml vs. 210.7 ng.h/ml) more than double that of those with normal kidney function. Adverse effects were experienced by 50% of patients with severe kidney failure vs. 14.3% in those with normal kidney function.
- In a case study of a single HD patient, oxycodone and its metabolites were reduced by dialysis, yet there was no loss of analgesia [96]. More recently, knowledge about the dialyzability of oxycodone comes from a study of 20 HD patients on stable doses of oxycodone CR [97]. Dialyzability of oxycodone and noroxycodone was possible but very limited. Not surprisingly therefore, there was no significant increase in postdialysis pain with no need for additional opioid dosing. This is not surprising as oxycodone has a relatively high volume of distribution (greater than hydromorphone), is nearly 50% protein bound, and is only moderately water soluble.

Hydrocodone

- A semisynthetic strong opioid synthesized from codeine: 99% of the world's supply is consumed in the United States, where it is the most commonly prescribed opioid, including for CKD patients.
- Primarily metabolized in the liver into several metabolites, including hydromorphone, via CYP2D6, therefore it might be expected to have a similar unpredictable risk of serious overdosing or underdosing after administration of standard doses, as seen with codeine and tramadol (Figure 74.1). In clinical practice this is less clear. The production of the active metabolite of hydrocodone (hydromorphone) is reduced in CYP2D6 "poor metabolizers" but there is little evidence of a difference in analgesic effect. Ultrarapid CYP2D6 metabolizers may have an increased response to hydrocodone with an increased risk of overdose.
- Approximately 26% is excreted in the urine either unchanged or as a metabolite, therefore kidney failure is hoped to have only a minimal effect on drug clearance. However, data are extremely limited as described below.
- There is only a single study that has assessed the extent to which varying degrees of kidney failure can affect the pharmacokinetics of hydrocodone and this involved a single 45 mg dose of extended-release formulation over 144 h [98]. All subjects received naloxone at 15 and 3 h before and 9 and 21 h postdose to minimize opioid-related adverse effects. There were eight patients with mild kidney failure (>50–80 ml/min), nine with moderate (30–50 ml/min), nine with severe (<30 ml/min), and nine on HD ≥6 mo. Systemic exposure was up to 70% greater in patients with moderate to severe kidney failure but appeared to be unchanged in patients on HD. There was no consistent trend toward an increase in maximum concentration of hydrocodone with increasing severity of kidney failure. However, the incidence of adverse effects in patients on dialysis was similar to that in those with normal kidney function despite the concurrent use of naltrexone.
- Without any data to support its use, and the high potential for unpredictable toxicity risk, it remains unclear the role that hydrocodone should or should not have in the pharmacologic management of pain for patients with advanced CKD.

AUC, area under the curve; C_{max}, maximum concentration; COX, cyclooxygenase; CYP, cytochrome P450; GI, gastrointestinal; GFR, glomerular filtration rate; HD, hemodialysis; NSAIDs, nonsteroidal anti-inflammatory drugs; SSRIs, selective serotonin reuptake inhibitors. Adapted from Davison [60] with permission.

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fore best reserved for specific indications of inflammatory acute pain, limiting their use to the lowest effective dose and shortest duration [85]. Topical NSAIDs can provide effective pain relief without the systemic adverse events associated with oral NSAIDs when used for both acute and chronic pain [100, 101]. Where pain is present in joints or nonulcerated skin, this may be a useful alternative to oral administration.

Opioids for Patients with Advanced CKD

Opioid Metabolism and Advanced CKD

Opioid metabolism takes place primarily in the liver, with the metabolites, and to varying degrees the parent drug, excreted by the kidneys. Metabolism produces both active and inactive metabolites, some of which may be more potent than the parent compound. These will accumulate to various degrees in patients with advanced CKD, increasing the risk of opioid toxicity.

Careful selection of opioids is essential and understanding opioid metabolism is important in this determination. The risks of adverse effects, poor analgesic response, and drug interactions are determined largely by which enzyme system (s) metabolize the opioid and the patient's genetics factors and medical conditions, most notably kidney or liver failure.

Opioids are metabolized in the liver in one of two ways as outlined in Figure 74.1 [60]. Phase 1 metabolism involves oxidation or hydrolysis of the drug primarily via cytochrome P450 2D6 (CYP2DP) and/or cytochrome P450 3A4 (CYP3A4) enzymes. Phase 2 metabolism involves conjugation of the drug.

People's responses to drugs that are metabolized via the CYP2DP enzyme are highly variable due to the tremendous genetic polymorphism of the *CYP2D6* gene. Individuals who have three or more active copies of the *CYP2D6* gene are described as "ultra-rapid metabolizers" whereas those who carry inactive copies of *CYP2D6* are "poor metabolizers." This can result in poor analgesic response with standard doses or unpredictable toxicity with trivial doses [87]. Opioids that are metabolized by the CYP3A4 enzyme have a high risk of drug–drug interactions as this enzyme metabolizes more than 50% of drugs. Concomitant use of CYP3A4 substrates and inhibitors can increase the parent opioid concentration, thereby prolonging analgesic effect or toxicity. Examples can be seen in Figure 74.2 [60]. CYP3A4 inducers can reduce opioid levels and therefore reduce analgesic effect. The CYP2D6 enzyme metabolizes approximately 25% of drugs so is associated with a lower risk of drug–drug interactions. Drugs that are metabolized by phase 2 glucuronidation have minimal drug interaction potential. While genetic variability exists, these drugs do not appear to have the same risk for unpredictable toxicity as seen with CYP2D6-mediated metabolism.

Recommended Opioids for Pain Management in Patients with Advanced CKD

The current available pharmacokinetic and pharmacodynamic evidence for those opioids considered safer to use in patients with advanced CKD has recently been reviewed and is summarized in Table 74.9 [60]. Given the minimal changes in pharmacokinetics in kidney failure, hydromorphone, fentanyl, methadone, and buprenorphine may be useful analgesics. Hydromorphone has the advantage of undergoing no phase 1 metabolism therefore avoiding the

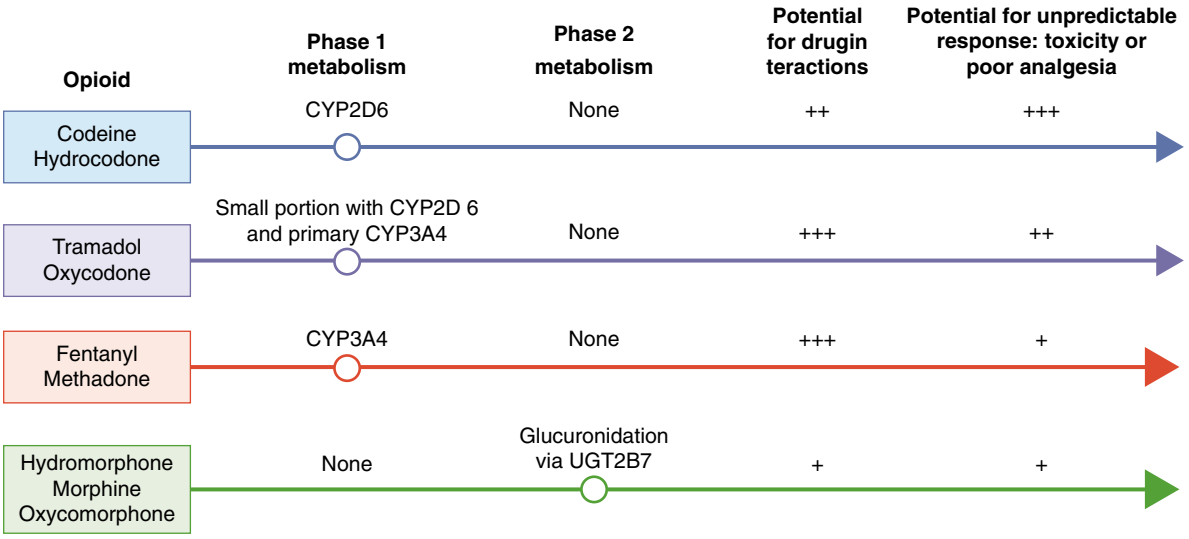

Figure 74.1 Opioid metabolism and the clinical implications. CYP2D, cytochrome P450 2D6 enzyme; CYP3A4, cytochrome P450 3A4 enzyme; UGT2B7, Uridine 5'-diphospho-glucuronosyltransferase-glucuronosyltransferase 2B7.

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	CYP3A4	CYP2D6	Potential effect
Substrate	• Calcium channel blockers • Statins • Other cardiovascular agents (quinidine) • Benzodiazepines • Sleep aids: zopiclone, zolpidem • Psychiatric drugs: haloperidol, carbamazepine, mirtazapine • Macrolide antibiotics • HIV antivirals	• Beta-blockers • Antipsychotic drugs (haloperidol) • SNRIs • Tricyclic antidepressants • Histamine H1 receptor antagonists (metoclopramide) • Tamoxifen	May increase the concentration, thereby prolonging analgesic effect or toxicity
Inhibitor	• Calcium channel blockers: specifically diltiazem and verapamil • Macrolide antibiotics • -azole antifungals • Grapefruit juice • Star fruit • HIV antivirals	• Antiarrhythmic agents: quinidine, amiodarone • SNRIs, SSRIs • Histamine H2 receptor antagonists: ranitidine, cimetidine • Bupropion • Cinacalcet	
Inducer	• Anticonvulsants: carbamazepine, phenytoin, barbiturates • Rifampin • St. John's wort	• Rifampin • Glucocorticoid: dexamethasone	May reduce opioid levels and therefore reduce analgesic effect

Figure 74.2 Some of the commonly used classes of drugs in patients with CKD that may act as substrates, inhibitors or inducers of CYP3A4 and CYP2D6 and therefore may impact opioid metabolism and effect. CYP2D6, cytochrome P450 2D6 enzyme; CYP3A4, cytochrome P450 3A4 enzyme; CCBs, calcium channel blockers; HIV, human immunodeficiency virus; TCAs, tricyclic antidepressants; SNRIs, serotonin-norepinephrine reuptake inhibitors. *Source:* Indiana University: The Flockhart Table. Retrieved from: http://medicine.iupui.edu/CLINPHARM/ddis/main-table, 2016. Last accessed 20 February 2019.

complications of unpredictable toxicity and drug–drug interactions seem with CYP2D6- and CYP34A-mediated metabolism. An additional consideration is the impact of the dialyzability of analgesics for those patients on dialysis. Opioids that are dialyzed will likely require supplemental dosing during or after dialysis and patients could be at higher risk for symptoms of opioid withdrawal after dialysis. Opioids that are not well dialyzed will have more stable analgesia. However, if there is accumulation of the parent drug and/or active metabolites, the risk for toxicity increases. Hydromorphone, fentanyl, methadone, and buprenorphine all appear to have a relatively stable analgesic effect during dialysis although their removal with dialysis varies, as seen in Table 74.9.

A Stepwise Approach to the Introduction and Titration of Analgesics

Figure 74.3 outlines the recommended stepwise approach to the pharmacologic management of pain for patients with advanced CKD [60]. Adjuvant therapy is the first step for people with a neuropathic component to their pain. In the general population, anticonvulsants and tricyclic antidepressants (TCAs) are the two classes of drugs for which there is the most evidence of efficacy [112, 113]. A small study showed improvement in pain and QoL scores for hemodialysis patients with diverse causes of neuropathic pain using gabapentin [114]. Gabapentin is almost exclusively cleared by the kidneys and substantial dose reduction is required as GFR declines to avoid toxicity. Adverse effects include somnolence, dizziness, peripheral edema, and gait disturbances. Gabapentin is cleared by hemodialysis and was recently found to be cleared slowly by continuous ambulatory peritoneal dialysis [115].

Evidence suggests carbamazepine may be as effective as gabapentin for treating neuropathic pain in the general population and, unlike gabapentin, requires no dose adjustment in CKD [115]. TCAs appear to be less well tolerated than the gabapentinoids in patients with CKD because of anticholinergic, histaminergic, and adrenergic side effects resulting in symptoms such as dry mouth, orthostatic hypotension, and somnolence. Although dose reduction of TCAs is not necessarily required in CKD, patients will often respond to lower doses. There are

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Table 74.9 The pharmacokinetics of opioids recommended for use in patients with advanced CKD.

	Hydromorphone	Fentanyl	Methadone	Buprenorphine
Clinical description	A potent μ receptor agonist that is ~5–7 times more potent than morphine following oral administration and ~3 times more potent following intravenous administration. It may cause less pruritus, sedation, and nausea than morphine.	A potent synthetic opioid that is 50–100 times more potent than morphine. It causes less histamine release, has a lower incidence of constipation, and affords greater cardiovascular stability than morphine.	A potent synthetic opioid with activity mainly at the μ receptor. It also appears to function as an NMDA receptor antagonist and therefore may be more effective for neuropathic pain than other strong opioids, although evidence to support this remains limited.	A potent semisynthetic opioid. It is a partial μ receptor agonist and a κ receptor antagonist.
Oral bioavailability	Low-moderate	Low: usually administered intravenously or transdermally	High	Low: administered effectively sublingually or transdermally.
Route of clearance	Extensive first-pass hepatic metabolism with little unchanged drug found in the urine. It is metabolized principally to H3G, which has no analgesic activity but possibly causes neuro-excitation, agitation, confusion, and hallucinations. Unlike morphine, which has an active analgesic 6-glucuronide metabolite, H6G is present in trace amounts only. The pharmacokinetics of the active parent compound are not substantially altered by CKD due to the rapid conversion to H3G [102].	Hepatic metabolism with 10–20% excreted by the kidneys. Metabolites are inactive.	Hepatic metabolism into inactive metabolites with ~20% excreted unchanged in the urine. In anuric patients, methadone is exclusively excreted in feces with no significant accumulation in plasma [103].	Extensive first-pass hepatic metabolism with little unchanged drug found in the urine [104]. The two major metabolites, B3G and norbuprenorphine, are mostly excreted fecally with only 10–30% excreted in the urine [105]. B3G is inactive with no analgesic properties. Norbuprenorphine is a less potent analgesic at the μ receptor than buprenorphine; its clinical relevance is thought to be limited as it does not cross the blood–brain barrier readily. A study with 10 HD patients showed no elevated buprenorphine or norbuprenorphine plasma levels receiving transdermal buprenorphine (median dose 52.5 μg/h) for at least 1 week [106].
Plasma half-life	Hydromorphone: unchanged with CKD H3G: prolonged	Unchanged with CKD	Unchanged with CKD However, prolonged pharmacological action due to slow release from tissue reservoirs of up to 60 h [107].	Unchanged with CKD

(*Continued*)

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Table 74.9 (Continued)

	Hydromorphone	Fentanyl	Methadone	Buprenorphine
Removal by HD	H3G accumulates between dialysis treatments but appears to be effectively removed during HD with no significant change in pain scores post-HD or a need for supplemental dosing [102, 108]	Not removed to any significant degree but there is the possibility of adsorption to CT190 dialysis membranes [109][a]	Parent drug and metabolites do not seem to be removed by HD: ~6.0 –14.9% reductions in plasma methadone [108, 110, 111]. No significant difference in pain scores post-HD and supplemental methadone is not required post-HD [108]. QT interval increased significantly: maximum 152 min after methadone intake. Remained <500 ms and was not linearly associated with serum methadone concentration, but may be exacerbated by HD reductions in serum potassium and/or magnesium [110].	HD does not appear to affect buprenorphine plasma levels, and analgesic effect is stable during HD [106]
Dosing recommendations	Start at 0.5 mg PO (or 0.2 mg subcutaneously) q4–6 h	Not recommended in opioid naïve patients. When converting from hydromorphone, 6-8 mg oral hydromorphone daily can be converted to 12 μg/h q72 h	Start 1–2 mg q12–24 h PO. Obtain a pre-treatment ECG and a follow-up ECG 2–4 weeks after initiation to monitor for prolonged QT interval.	Start at 5 μg/h q7 d

B3G, buprenorphine-3-glucuronide; H3G, hydromorphone-3-glucuronide; H6G, hydromorphone-6-glucuronide; HD, hemodialysis; ESKD, end-stage kidney disease; NMDA, N-methyl-D-aspartate; PO, per os; ECG = electrocardiogram.

[a] Based on data from a single chronic hemodialysis patient.Adapted from Davison [60] with permission.

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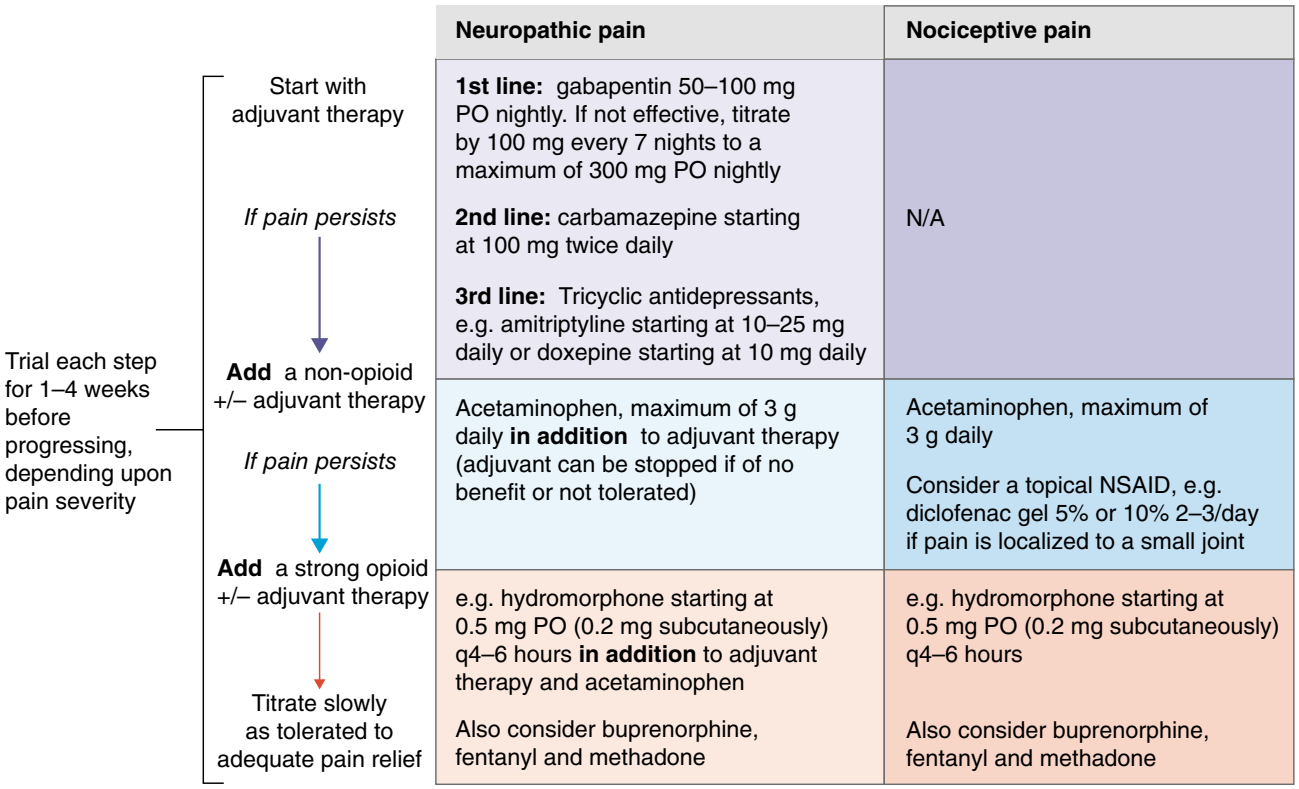

Figure 74.3 A stepwise approach to the management of pain in patients with advanced CKD. PO, per os; TCAs, tricyclic antidepressants; NSAID, nonsteroidal anti-inflammatory drug.

insufficient data or clinical experience with selective serotonin reuptake inhibitors and selective serotonin norepinephrine reuptake inhibitors for neuropathic pain in CKD to make a recommendation.

The anesthetic ketamine is an analgesic in subanesthetic doses. Ketamine is a potent N-methyl-D-aspartate (NMDA) receptor channel antagonist. Clinically, it is reserved for intractable chronic pain syndromes, especially those with a neuropathic component that are resistant to opioids and basic adjuvants. An example is the management of the pain of calciphylaxis (Specific Pain Syndromes in Patients with Advanced CKD). There is no need for dose adjustment in CKD [116]. Two reviews of ketamine for chronic noncancer pain (including neuropathic and ischemic pain) concluded that ketamine provides good analgesia but that adverse events such as psychotomimetic effects and tachycardia may limit its use [117, 118]. A systematic review of analgesia for phantom limb pain reached similar conclusions [119]. To eliminate or reduce the risk of psychotomimetic effects, the concurrent administration of haloperidol or midazolam is recommended [120].

Nonopioids should be used as initial pharmacologic management for nociceptive pain and for neuropathic pain if pain persists despite the maximal tolerated dose of an adjuvant. These drugs should be used to their full potential before moving on to a stronger analgesic. For patients with advanced CKD, there are no weak opioids considered suitable or safe for use so it is recommended to add a very low dose of a strong opioid. Weak opioids have the same dose-dependent adverse effects as strong opioids and there is no evidence that weak opioids are less risky than strong opioids if the strong opioid is used at its lowest effective dose [132]. A recent study of 140 899 adult hemodialysis patients in the United States showed the highest hazards for altered mental status, falls, and fractures were associated with codeine rather than the strong opioids [80]. There is also no evidence that at equivalent analgesic efficacy weak opioids carry a lower risk of addiction than low-dose strong opioids.

End-of-life Pain Management and Special Considerations

A critical aspect of the care of the dying patient with advanced CKD is vigilance about pain and its management. Near the end of life, swallowing becomes compromised and alternate routes for analgesic administration are required. Given that patients are often unconscious and not able to articulate the severity of their pain, physicians

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should regularly enquire of nursing staff or families whether the patient appears distressed, especially on routine turning in bed. A person who enters the terminal phase with analgesia needs to have this continued throughout and not ceased prematurely. An algorithm for terminal pain management is presented in Chapter 55. In this situation the use of parenteral opioids is preferred, with fentanyl being the medication of choice. If pain is solely or predominantly neuropathic in origin and the patient is no longer able to swallow, there is good evidence for the use of parenteral lidocaine [121].

Specific Pain Syndromes in Patients with Advanced CKD

Autosomal Dominant Polycystic Kidney Disease

Autosomal dominant polycystic kidney disease (ADPKD) may cause acute or chronic pain. It is estimated that up to 70% of patients experience severe pain not controlled by oral analgesia [122]. Acute pain may result from cyst infections, cyst rupture or nephrolithiasis. Both recurrent pain and chronic pain may result from intrarenal causes (capsular distension, traction on the renal pedicle) or extrarenal pressure on other organs, nerve plexuses or structures, such as the lumbar vertebrae. Patients may concurrently have hepatic cysts that, of themselves, can cause severe pain.

As Lanktree and Chapman state, "there is no gold standard modality for pain in ADPKD" [123]. The management of pain secondary to ADPKD consists of three modalities:

1) *Nonpharmacological treatment*: This includes massage, heat packs, and psychological strategies and support [124].
2) *Pharmacological*: Acetaminophen may be all that is required or, if the pain is more severe, a combination of opioids and agents for neuropathic pain [124, 125].
3) *Procedural*: This includes minimally invasive interventions, such as cyst aspiration, cyst decortication, and renal denervation, or invasive interventions, such as partial or, as an "absolute last resort" [123], total nephrectomy.

Calciphylaxis

Calciphylaxis (calcific uremic arteriolopathy) is a rare complication of end-stage kidney disease (ESKD) in which metastatic calcification of small and medium-sized vessels causes ischemic necrosis in the skin and subcutaneous tissue, resulting in intense, severe pain disproportionate to the size of the lesions. Calciphylaxis is associated with a high mortality rate: 1 year mortality rates are reported as 45–80% [126,127]. Management of calciphylaxis includes analgesics, intradialytic sodium thiosulphate, hyperbaric oxygen, and in certain circumstances the amputation of affected limbs.

The pain of calciphylaxis is notoriously difficult to manage. Authorities on this condition recommend the involvement of a multidisciplinary team including the participation of specialists in both pain medicine and palliative care [128]. There are no randomized controlled trials to help guide treatment. Nevertheless, there are several consistent observations in published case reports. First, it is thought that the pain of calciphylaxis has both ischemic and neuropathic components [130]. This helps explain why the pain tends to be only partially opioid responsive [130]. The singular use of opioids and their escalation up to the point of toxicity is fruitless [130]. A degree of analgesia was only achieved in the case reports with simultaneous administration of adjuvant medications for neuropathic pain (such as ketamine) [130, 131]. The final observation is the importance of timely, robust, and regular reassessments of pain to guide the titration of analgesics to reflect the rapid escalation in pain and distress of the patient. Treating the pain of calciphylaxis as a pain emergency reflects the appropriate level of gravity clinicians should place on this condition.

Conclusions

Pain is a highly complex and personal phenomenon with far-reaching physical and psychosocial consequences if it progresses to become a chronic disorder. A summary of the recommendations discussed in this chapter is given in Table 74.10. A multidisciplinary pain team is best positioned to manage chronic pain if it is resistant to simple interventions. The first-line management of chronic pain is a nonpharmacological approach that includes patient education, exercise, weight reduction, thermal therapy, yoga, acupuncture, and CBT as appropriate along with a clear understanding of the patients' goals and expectations for therapy. Pharmacologic treatment should only be used to augment nonpharmacologic therapies as required to meet patient-specific treatment goals. In the context of advanced CKD and the multimorbidity that many patients experience, they will have numerous reasons for ongoing pain and will most likely require some analgesic therapy. This requires the careful selection of analgesics with very close attention to efficacy and safety, keeping in mind the overall goal is to promote functionality and QoL, and not necessarily completely resolve the pain. We suggest that prior to commencing opioids patients be screened for substance use disorder and for those who are considered to be at high risk, naloxone be prescribed and the patient followed by a pain specialist.

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Table 74.10 Practice recommendations for a general approach to pain management for patients with advanced CKD.

Treatment	Recommendation	Certainty of evidence	Strength of recommendation
Screening for substance use disorder	We suggest that prior to commencing opioids patients be screened for substance use disorder	Low	Weak
Multidisciplinary pain management	We suggest that chronic pain, if resistant to simple interventions, be managed by a multidisciplinary pain team	Low	Weak
Nonpharmacological management of chronic pain	We suggest that the first-line management of chronic musculoskeletal pain is a nonpharmacological approach. This includes education, exercise, weight reduction, thermal therapy, yoga, acupuncture, and cognitive behavior therapy as appropriate.	Low-moderate	Weak
Interventional	We suggest that an epidural injection be considered in chronic spinal pain resistant to other interventions	Moderate	Weak
Pharmacological management of chronic pain	We suggest that pharmacologic treatment of chronic pain should only be used to augment nonpharmacologic therapies as required to meet patient-specific treatment goals	Moderate	Weak
Naloxone	We suggest that patients who are prescribed opioids and are assessed as high risk for substance abuse disorder be prescribed naloxone and be followed by a pain specialist	Low	Weak

GRADE assessment of the certainty of evidence: High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different* is low. Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different* is moderate. Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different* is high. Very low: This research dies not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different* is very high. **Substantially different = a large enough difference that it might affect decision-making*.

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75

Neurocognitive Disorders

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Introduction

Neurocognitive disorders are primarily disorders of cognition that are acquired and represent a significant decline from previous functioning that is not due to delirium, another psychiatric condition, or developmental disorders. Neurocognitive disorders are subclassified as major or mild based on whether activities of daily living are affected. Major neurocognitive disorder is evidence of significant cognitive decline on one or more cognitive domains that interferes with independent activities of daily living. Mild neurocognitive disorder is evidence of one or more cognitive deficits without loss of independent functioning. The Diagnostic and Statistical Manual of Mental Disorders replaced the term "dementia" with "major neurocognitive disorder" in 2013 [1]. Neurocognitive disorders are characterized by cognitive impairment as their core feature, while the term "neuro" indicates they relate to brain disease and altered brain function.

Six distinct cognitive domains can be affected in mild or major neurocognitive disorder (Table 75.1) and may be differently affected by pathological processes. These domains are executive function, complex attention, social cognition, learning and memory, language, and perceptual-motor function. Numerous assessment tests for neurocognitive functioning are used, and range in their focus and scope. Cognitive screening tools can be influenced by age, educational level, and language fluency. Screening assessments may have published language- and age-specific norms that can allow standardization across populations. To our knowledge, there has been no systematic evaluation of the diagnostic test accuracy for cognitive functioning assessment applied to adults with chronic kidney disease. Single studies suggest that the Montreal Cognitive Assessment (MoCA) correlates with a full neurocognitive battery of tests and detects neurocognitive disorders in dialysis patients, while the Mini-Mental State Examination (MMSE) is weakly discriminating for neurocognitive dysfunction [4, 5].

Cognitive impairment in chronic kidney disease is related to vascular and nonvascular mechanisms leading to microvascular injury, and white matter loss and microinfarction. Magnetic resonance imaging among patients with kidney disease demonstrates large vessel ischemia, small vessel lacunar infarction, and white matter lesions arising from small vessel ischemia [6–8]. Nonvascular factors that may be associated with cognitive functioning in chronic kidney disease include anemia, uremia, oxidative stress, intradialytic hypotension, dialysis disequilibrium, hyperviscosity, and vascular calcification [9].

Knowledge of the prevalence of neurocognitive disorders in children with chronic kidney disease is limited due to the high risks of selection and measurement biases in existing studies [10]. Global cognition of children with chronic kidney disease is low average, and varies by severity of kidney disease. Children treated with dialysis are most severely affected, showing significantly lower global cognitive functioning than children with mild-moderate chronic kidney disease and pediatric recipients of a kidney transplant. Children with chronic kidney disease have lower scores in executive function and verbal and visual memory domains, and lower academic skills, including mathematics, reading, and spelling.

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Table 75.1 Cognitive domains.

Domain	Subdomains	Examples of everyday activities
Complex attention	Sustained attention; divided attention; selective attention; processing speed	Normal tasks take longer, especially when there are competing stimuli; easily distracted; tasks need to be simplified; difficulty holding information in mind to do mental calculations or dial a phone number
Executive function	Planning; decision-making; working memory; responding to feedback; inhibition; flexibility	Difficulty with multistage tasks, planning, organizing, multitasking, following directions, keeping up with shifting conversations
Learning and memory	Free recall; cued recall; recognition memory; semantic and autobiographical long-term memory; implicit learning	Difficulty recalling recent events, repeating self, misplacing objects, losing track of actions already performed, increasing reliance on lists and reminders
Language	Object naming; word finding; fluency; grammar and syntax; receptive language	Word-finding difficulty, use of general phrases or wrong words, grammatical errors, difficulty with comprehension of others' language or written material
Perceptual-motor function	Visual perception; visuoconstructional reasoning; perceptual-motor coordination	Getting lost in familiar places, more use of notes and maps, difficulty using familiar tools and appliances
Social cognition	Recognition of emotions; theory of mind; insight	Disinhibition or apathy, loss of empathy, inappropriate behavior, loss of judgment

Source: Adapted from American Psychiatric Association [1], Eramudugolla et al. [2], and Hugo et al. [3].

Adults with chronic kidney disease (defined as an estimated glomerular filtration rate below 60 ml/min/1.73 m^2) perform worse than people without chronic kidney disease on orientation and attention, language, concept formation and reasoning, executive function, memory, and global cognition. The evidence for cognitive function in people with kidney disease is limited by risks of bias in available studies as well as clinical and statistical heterogeneity in the existing literature base [11]. Cognitive functioning may fall in parallel with kidney function decline, with specific cognitive domains differentially affected. Notably, cognition (both self-perceived and measured) can alter decision-making of dialysis modality choice and be linked to lower use of self-care dialysis modalities and treatment adherence [12]. Cognitive decline occurs before measurable loss in kidney function [13].

Evaluation of neurocognitive disorder includes identifying potentially reversible causes such as severe uremia, depression, electrolyte disturbances, aluminum toxicity, and neuroactive medication toxicity. Presently, there are few randomized trials in which cognitive function is a clinical endpoint. Specific disease-modifying agents such as cholinesterase inhibitors have not been adequately tested in the presence of chronic kidney disease. Social support, shared decision tools, and advance care planning are especially relevant to the care of adults with chronic kidney disease and a neurocognitive disorder, although high-certainty evidence for their use is lacking.

This chapter examines the evidence for screening and management of neurocognitive disorders in adults and children with chronic kidney disease.

Definition

Neurocognitive disorders are a decline in cognitive functioning in one or more cognitive domains from a previous level of performance. A decline in function is greater than that expected by aging needs to be acquired rather than developmental and not due to an alternative psychiatric condition or delirium. The decrease in functioning should be documented by concern expressed about significant decline by an individual who knows the patient or is observed by a clinician together with impairment documented by standardized neuropsychological testing [1]. Major neurocognitive disorder is characterized by interference with independence in everyday activities, while mild disorder is characterized by independent daily living, although activities may require additional time and effort, support, or compensatory activities. While neurocognitive disorders in the general population require further specification by likely etiology, chronic kidney disease might be considered an explanatory etiology based on the characteristics cerebral imaging findings consistent with predominantly microvascular disease. The *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition details six cognitive domains which may be affected, including complex attention, executive function, learning and memory, language, perceptual-motor function, and social cognition. Dementia is the equivalent of major neurocognitive disorder.

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Epidemiology

Many studies have evaluated the prevalence of neurocognitive disorders among people with chronic kidney disease, although summary estimates are uncertain due to the statistical and clinical heterogeneity in the study populations and diagnostic tools used to assess neurocognitive disorders, in addition to the high risks of methodological bias limiting confidence in the findings. The prevalence of neurocognitive disorders is dependent on evidence of decline from a previous level of functioning, which is challenging to measure on a large scale for observational analysis.

The prevalence and severity of neurocognitive disorders and the pattern of altered cognition across the six cognitive domains varies in adults and children, by severity of chronic kidney disease, and in the context of dialysis treatment. Based on a meta-analysis of cohort and cross-sectional studies, children and young adults with chronic kidney disease are shown to experience lower IQ (global, verbal, and performance) compared with their peers, with greater reductions among those treated with long-term dialysis and intermediary values for pediatric recipients of a kidney transplant [10]. Children with mild-moderate chronic kidney disease have impaired behavior regulation, metacognition, and global executive functioning, while deficits are less consistently observed among transplant recipients. Children with chronic kidney disease also show impaired verbal and visual memory. In parallel, children and young adults with chronic kidney disease have lower academic achievement in reading, arithmetic, and spelling, with those on dialysis most severely affected. Neurocognition appears to decrease in children as kidney function declines and impacts children most who have experienced a prolonged duration of kidney disease.

In adults, as in younger persons, neurocognitive functioning is related to severity of kidney function, appears to decrease with lower glomerular filtration rate, and is related to the presence of dialysis [11]. Adults with chronic kidney disease perform worse than those without chronic kidney disease on orientation and attention, language, concept formation and reasoning, executive function, memory, and global cognition, with loss of executive function greatest when the glomerular filtration rate is below 30 ml/min/1.73 m^2. People treated with hemodialysis have worse cognition THAN the general population in the domains of attention, memory, construction and motor functioning, executive functioning and global cognition. There was limited evidence of consistent clinical differences in neurocognitive functioning for hemodialysis patients compared with those treated with peritoneal dialysis or those with end-stage kidney disease and not dialyzed. Study limitations, however, reduced certainty and precision in the ESTIMATED prevalence of neurocognitive disorders in each of these populations [14].

In a study of 374 hemodialysis patients older than 55 years, cognitive functioning in the domains of memory, executive function, and language indicated that nearly 40% had severe impairment and approximately 35% had moderate impairment. Notably, only 3% had previously documented deficits, and neurocognitive disorder was linked to cerebrovascular disease, dialysis dose, and prior educational attainment [15].

Kidney transplantation is linked to moderate to large improvements in the domains of general cognitive function, information and motor processing, spatial reasoning, and verbal and visual memory when compared with functioning in the pre-operative period [16]. Transplanted patients have better cognitive functioning than dialysis-dependent controls and those treated without dialysis. Cognitive performance among transplanted individuals remains lower than in people without chronic kidney disease in the domains of executive functioning, verbal fluency, and language. By contrast, changing from conventional thrice-weekly hemodialysis to frequent nocturnal hours hemodialysis is not associated with clinically important improvements in cognitive functioning [17].

Pathophysiology

Neurocognitive impairment is multifactorial in chronic kidney disease (Figure 75.1). The precise neuropathology is unknown, although it is thought that microvascular pathologies predominate, while direct neuronal injury also occurs. Cerebral imaging among patients with chronic kidney disease reveals a substantial burden of ischemic stroke, small vessel (lacunar) infarction, and white matter changes caused by ischemia. The linked risks of cerebral small vessel disease and end-stage kidney disease for patients with type 2 diabetes suggest that the two conditions may share a common pathological process [19]. The pathological vascular processes in the neurocognitive disorder of chronic kidney disease that cause reduced white matter volume and integrity are distinct from the neurodegenerative processes seen in Alzheimer's disease, which is manifest as hippocampal atrophy. Patients with chronic kidney disease and end-stage kidney disease can also have Alzheimer's disease, but vascular pathologies are more common. Cerebral vascular disease may be superimposed on a neurodegenerative process and be further mediated by uremia, medications, hypoperfusion during dialysis, oxidative stress, and volume and electrolyte changes. Adults with

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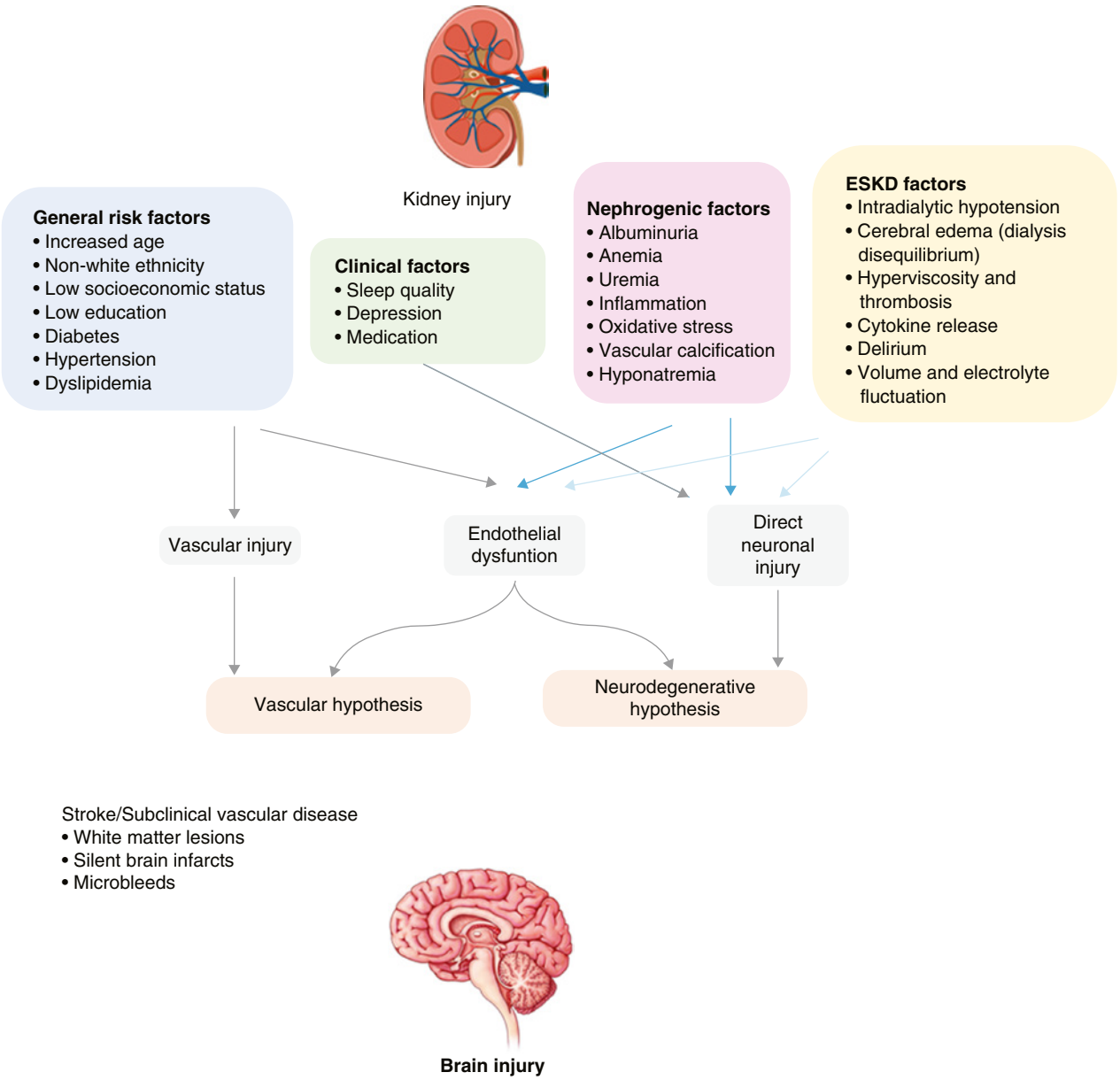

Figure 75.1 Risk factors associated with neurocognitive disorders in chronic kidney disease. *Source:* Adapted from [9, 18].

chronic kidney disease have traditional risk factors for cognitive impairment, including age, lower educational attainment, diabetes, hypertension, dyslipidemia, and non-white ethnicity.

In addition to the traditional risk factors shared with the wider population, clinical factors specific to renal disease are present that are associated with neurocognitive problems. These include a high prevalence of depression, adverse effects of medications or their interactions, fatigue and poor sleep quality, and anemia. Chronic kidney disease increases oxidative stress, cytokines, and inflammation, which may accelerate vascular disease and small vessel cerebral infarction.

End-stage kidney disease and the actual process of dialysis can potentiate cerebral vascular changes including volume and electrolyte shifts and related dialysis-disequilibrium. Dialysis may lead to hypotension and cerebral hypoperfusion, exacerbating the tendency to microvessel infarction. Extracorporeal blood flow incurs intravascular thrombosis, which can be potentiated by fluid removal and hyperviscosity. Hyperparathyroidism may lead to altered cerebral calcium and vascular dysfunction [20].

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The observation that kidney transplantation provides a sustained improvement in cerebral functioning is supported by the finding of reduced latency and increased amplitude of cortical potentials throughout the brain. These suggest that the active alleviation of uremia and associated phenomena by normalization of kidney function may lead to improved neurocognitive performance [21].

In children, uremia may be associated with periventricular white matter changes, cortical atrophy, slower nerve conduction, and impaired myelination and synaptic development [22].

Diagnosis

The clinical diagnosis of neurocognitive disorders is based on reporting of concern by a reliable informant or clinician together with standardized neuropsychiatric assessment. A central component of a diagnosis is demonstration of decreased functioning over time, more than the normal aging process.

Clinical History

At the start of a clinical assessment, it is important to be aware that a patient may or may not have recognized any change, and the neurocognitive issue has been highlighted by a family member or care giver. Family members may attribute changes to the normal aging process or not recognize a slowly progressive process. In contrast to neurocognitive disorders, cognitive changes due to aging consist of isolated changes in memory or information processing and often fail to progress. Patients with a neurocognitive disorder may demonstrate difficulty holding on to new information, get lost in familiar or unfamiliar surroundings, not complete complex tasks that they were previously able to, have problems with reasoning such as dealing with treatment choices, have difficulty finding words, or show new unexpected behaviors.

The initial clinical assessment of the patient will include obtaining a full and complete history of the timing of the changes in cognition and behavior from both the patient and the informant, in addition to a medical history exploring medications, particularly medications that may impact cognition. Assessment for depressive symptoms, anxiety, and delirium is required.

Neurocognitive Tests

Cognitive testing is an important component of the clinical assessment to corroborate the history. A combined assessment of the history (indicative of the longitudinal progression of signs and symptoms) together with cognitive testing suggesting abnormalities in one or more cognitive domains underpins the diagnosis. There is a wide range of neurocognitive tests, none of which are specifically designed to assess all cognitive domains simultaneously or used routinely in nephrology care. A comprehensive battery of tests is required to examine all areas of cognitive performance, although these can be time-consuming and resource-intensive to administer.

The most commonly-used screening tools for cognitive function in chronic kidney disease are the MMSE [23], the MoCA [24], and the Trail Making Test [25]. The MMSE is a simple 30-point questionnaire and requires a short interview to gather information on orientation, visual and auditory memory, attention, language, comprehension, and visual construction. The MMSE has low sensitivity for neurocognitive disorders and is particularly poor at detecting executive dysfunction in dialysis patients [4, 5]. The MoCA has higher sensitivity for mild neurocognitive disorder and executive function, which are both particularly relevant in chronic kidney disease. It is a brief screening instrument composed of 12 items assessing visuospatial and executive function, naming, attention, abstraction, short-term memory, and orientation. The Trail Making Test is a test of visual attention and task switching to provide information about visual search, scanning, speed of processing, cognitive flexibility, and executive function.

There is limited evidence for the diagnostic test accuracy of screening tools for neurocognitive disorder in chronic kidney disease. In a small study with 30 patients receiving hemodialysis and 30 matched controls, neurocognitive deficits in attention, visuospatial performance, language, memory, and executive function were documented using 13 cognitive measures [26]. While half of hemodialysis patients showed scores greater than 1 standard deviation (SD) below the mean across the domains, the average score on the MMSE and corresponding *z*-scores for the MMSE based on normative data were not different from controls, while the total MoCA scores were statistically significantly lower, explaining 66% of the variance in cognition measured by the comprehensive battery. This suggests the MMSE may lack sensitivity to identify neurocognitive deficits in the presence of end-stage kidney disease.

A more extensive battery of neurocognitive testing can explore the cognitive domains, although these require more specialist knowledge to conduct and interpret. A list of these tests categorized according to cognitive domain is shown in Table 75.2. Evidence is lacking for the diagnostic test accuracy for these tests to assess neurocognitive function in the presence of chronic kidney disease.

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Table 75.2 Examples of cognitive assessments as noted in the *Diagnostic and Statistical Manual* 5th edition.

Cognitive domain	Objective assessment	Example	Measures
Complex attention	Sustained attention	Press a button every time a tone is heard, over a period	Symbol digit modalities
	Selective attention	Hear numbers and letters but count only numbers	Trail Making Test A
	Divided attention	Tap rapidly while learning a story	Simple reaction time
	Processing speed	Carry out any timed task	Choice reaction time
Executive function	Planning	Maze puzzles, interpret sequential pictures, or arrange objects in a sequence	Digit span backwards Trail Making Test b
	Decision-making with competing alternatives	Simulated gambling	Stroop color word test
	Working memory	Hold information for a brief period and manipulate it, e.g., repeat a list of numbers backward	Zoo map (bads) Game of dice test
	Feedback utilization	Use feedback on errors to infer rules to carry out tasks	Go no-go test
	Inhibition	Override habits; choose the correct but more complex, less obvious solution, e.g. read printed names of colors rather than naming the color in which they are printed	
	Cognitive flexibility	Shift between sets, concepts, tasks, rules, e.g. alternate between numbers and letters	
Language	Expressive language	Naming of, e.g., objects or pictures; fluency for words in a given category (e.g. animals) or beginning with a given letter, in a limited time period (e.g. 1 min)	Letter fluency Boston naming test Spot the word test
	Grammar and syntax	Using articles, prepositions, helper verbs	
	Receptive language	Comprehend/define words, carry out simple commands	
Learning and memory	Immediate memory	Repeat a list of words or digits	California verbal learning test Benton visual retention test
	Recent memory	Free recall: recall as many items as possible from a list of words or a story or a diagram Cue recall: with an examiner providing cues, e.g. "recall as many food items as you can from the list" Recognition: with examiner asking, e.g. "was there an apple on the list?"	
	Semantic memory	Recall well-known facts	
	Autobiographical memory	Recall personal events	
	Implicit (procedural) memory	Recall skills to carry out procedures	
Perceptual-motor function	Visuoconstructional reasoning	Draw, copy, assemble blocks	Purdue pegboard test
	Perceptual-motor coordination	Insert blocks or pegs into appropriate slots	Benton visual retention copy
	Praxis	Mime gestures such as "salute" or actions such as "use hammer"	Ideomotor praxis
	Gnosis	Recognize faces and colors	
Social cognition	Recognize emotions	Identify pictures showing happy, sad, scared, angry faces	Reading the mind in the eyes test
	Theory of mind	Consider another person's thoughts, intentions when looking at story cards	

Source: Adapted from American Psychiatric Association [1], Eramudugolla et al. [2], and Hugo et al. [3].

Imaging

Neuroanatomical imaging in patients with chronic kidney disease shows white matter changes, and ventricular and hippocampal atrophy with more severe changes observed among patients with greater global cognitive impairment [27]. In three-dimensional magnetic resonance imaging, hemodialysis patients may have more severe neuroimaging abnormalities THAN those treated with peritoneal dialysis. In arterial-spin labeling magnetic resonance imaging, a noninvasive technique to

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evaluate cerebral blood flow changes, cerebral blood flow is reduced in dialysis patients and may correlate with hemoglobin levels [28]. In adults with diabetes, glomerular filtration rate or albuminuria correlated with gray matter volume suggesting neuroanatomical changes may occur early in chronic kidney disease [29].

Overall, for children and young adults with chronic kidney disease, lower gray matter and higher white matter volumes may occur in some cortical regions, but these can be relatively subtle and do not appear to correlate with cognitive impairments, suggesting a potentially functional rather than structural basis to neurocognitive difficulties in childhood chronic kidney diseases [30].

The evidence for using neuroanatomical or neurofunctional imaging to detect neurocognitive disorders and their subtype in chronic kidney disease is currently of very low certainty due to a lack of systematic evaluation of the available data. Neuroanatomical imaging can rule out alternative diagnoses.

Treatment

Although cognitive disorders are highly prevalent in people with chronic kidney disease, the evidentiary basis for management to improve clinical outcomes remains largely absent (Table 75.3). Systematic reviews of the evidence are principally limited to characterization of disease prevalence, patterns, and severity together with impact on prognosis and functioning. A systematic review and meta-analysis of potential treatments was not identified to guide clinical decision-making for management, patient or caregiver support, or therapeutic interventions specifically in adults or children with chronic kidney disease.

In this chapter, potential interventions are discussed together with a summary of the current level of evidence (Table 75.3).

Screening

At present, there is no high-level evidence that screening for neurocognitive disorders in adults or children with chronic kidney disease improves clinical endpoints.

Cognitive Remediation

There is little or no randomized controlled trial evidence for cognitive rehabilitation or remediation among children or adults with chronic kidney disease. Although not necessarily generalizable to chronic kidney disease, evidence among adults with stroke shows there are insufficient data to confirm or refute the long-term effects of cognitive rehabilitation on functional outcomes [31]. Similarly, adults with stroke may report short-term subjective improvement in memory with cognitive rehabilitation, but persistent effects on memory are not proven [32, 33]. For adults with stroke or nonprogressive brain injury, there is no high-quality evidence that cognitive rehabilitation alters executive functioning [34].

At present, there is no high-quality evidence for cognitive remediation interventions for children with chronic kidney disease and the data are generated in children with other learning or cognitive difficulties. Candidate interventions include age-specific cognitive remediation programs designed to improve attention and working memory, attention and executive function, attention and memory, and attention, memory, processing speed, social cognition, social navigation, and intelligence [35]. Randomized trials have evaluated cognitive remediation strategies in the settings of attention deficit hyperactivity disorder, learning disabilities, trisomy 21, low birth weight, post-traumatic stress disorder, and traumatic brain injuries. As the burden of kidney disease includes loss of schooling time and time-intensive therapies, evaluation of online remediation programs focused on academic outcomes would be appropriate.

Support Interventions for Caregivers

As patients with chronic kidney disease may be unaware of neurocognitive changes, evidence on the role of caregiver support in functional outcomes related to cognitive problems would be informative. The present evidence for support of informal caregivers is extremely limited and unable to inform clinical practice. Outcomes measured in such research is limited to caregiver knowledge [36].

In the general population, there is no high-quality evidence for the benefits of respite care for adults with neurocognitive disorders [37]. Similarly, there is little evidence for telephone counseling support for caregivers [38]. Cognitive reframing may reduce caregiver anxiety, depression, and subjective stress, but there is no good-quality evidence for improved coping, burden of care, reactions to behaviors, or institutionalization of the person with a neurocognitive disorder [38]. There is some information that case management may assist reducing admission to institutional care and overall health costs in the medium term among people with major neurocognitive disorders [39].

Decision Aids

Neurocognitive disorders in adults with chronic kidney disease alter decision-making about dialysis treatment and reduce self-care dialysis. There is no high-quality evidence

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Table 75.3 Treatment for neurocognitive disorders in adults and children with chronic kidney disease.

Treatment	Recommendation	Certainty of evidence	Strength of recommendation
Screening	We suggest that the certainty of the evidence for screening to manage neurocognitive disorders is so low that a recommendation regarding use in clinical practice is too speculative	Very low or absent (data from randomized controlled trials are absent)	No recommendation
Cognitive remediation or rehabilitation	We suggest that the certainty of the evidence for cognitive remediation or rehabilitation to manage neurocognitive disorders is so low that a recommendation regarding use in clinical practice is too speculative	Very low or absent	No recommendation
Support interventions for caregivers	We suggest that the certainty of the evidence for support interventions for caregivers to manage neurocognitive disorders is so low that a recommendation regarding use in clinical practice is too speculative	Very low or absent	No recommendation
Decision aids	We suggest that the certainty of the evidence for decision aids to manage neurocognitive disorders is so low that a recommendation regarding use in clinical practice is too speculative	Very low or absent	No recommendation
Depression treatments	We suggest that the certainty of the evidence for depression treatment to manage neurocognitive disorders is so low that a recommendation regarding use in clinical practice is too speculative	Very low or absent	No recommendation
Cholinesterase inhibitors and *N*-methyl D-aspartate receptor antagonists	We suggest that the certainty of the evidence for cholinesterase inhibitors and *N*-methyl D-aspartate receptor antagonists to manage neurocognitive disorders is so low that a recommendation regarding use in clinical practice is too speculative	Very low or absent	No recommendation
Vascular risk factor management	We suggest that the certainty of the evidence for vascular risk factor management to manage neurocognitive disorders is so low that a recommendation regarding use in clinical practice is too speculative	Very low or absent	No recommendation
Kidney transplantation	We suggest that the certainty of the evidence for kidney transplantation is low (based on a consistent and temporal association in nonrandomized studies) such that transplantation may be considered as a clinical practice that may improve neurocognitive functioning for people with chronic kidney disease	Low	Low
Longer hours or frequent hemodialysis	We suggest that the certainty of the evidence for longer hours or more frequent hemodialysis to manage neurocognitive disorders is low. Frequent or longer hours hemodialysis may make little or no difference to neurocognitive disorders in adults with CKD. Data for children are limited.	Low	Low
Anemia treatment	We suggest that the certainty of the evidence screening to manage neurocognitive disorders is so low that a recommendation regarding use in clinical practice is too speculative	Very low or absent	No recommendation

These recommendations reflect a belief that most adults, children, and their caregiver would place a high value on avoiding risks of adverse events and uncertain treatments. GRADE assessment of the certainty of the evidence: High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different* is low. Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different* is moderate. Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different* is high. Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different* is very high. **Substantially different = a large enough difference that it might affect decision-making*.

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for the use of decision aids to assist in decision-making about dialysis treatment or end-of-life care for people with chronic kidney disease and neurocognitive deficits. In older adults without cognitive impairment, decision aids may increase knowledge and risk perception, lower decisional conflict, and increase patient participation in the decision process [40]. The evidence to support palliative care interventions including decision aids, advance care planning, and end-of-life care in severe dementia is currently lacking and insufficient to inform care [41].

Therapy for Depression

Depression and neurocognitive disorders may coexist in chronic kidney disease. At present, there is no evidence that pharmacological or psychosocial interventions improve neurocognitive function in chronic kidney disease [42, 43].

Physical Activity

There is no high-quality evidence for exercise on neurocognitive functioning in chronic kidney disease, although a pilot study suggests exercise training during dialysis may help to preserve neurocognitive function [44]. There is no high-level evidence that aerobic exercise or increased fitness improves cognitive performance in older people, although potential benefits of high-intensity exercise have not been excluded [45]. Similarly, evidence is lacking for exercise in adults with major neurocognitive deficits.

Cholinesterase Inhibitors and *N*-Methyl D-Aspartate Receptor Antagonists

There are no high-level data published on cholinesterase inhibitors (tacrine, donepezil, rivastigmine, and galantamine) and *N*-methyl D-aspartate receptor antagonists (memantine), which are indicated for Alzheimer's disease and dementia with Lewy bodies and for major neurocognitive impairment [46]. Evidence of long-term benefits for these agents is currently limited for vascular disease-related neurocognitive deficits and may lead to withdrawal due to side effects in a substantial proportion of patients [47, 48].

Vascular Risk Factor Management

There is existing moderate or high certainty evidence that statin therapy and blood-pressure lowering therapy reduces cardiovascular events and death in adults with chronic kidney disease [49, 50], although evidence in dialysis patients suggests limited benefit for cholesterol-lowering therapy and treatment estimates for transplant recipients are imprecise [51]. The evidentiary basis for vascular risk factor management on neurocognitive functioning in chronic kidney disease is absent. There is high-quality evidence that statins given in later life to people at risk of vascular disease do not modify cognitive decline or major neurocognitive disorders [52].

Transplantation

Kidney transplantation is temporally associated with sustained but incomplete improvements in neurocognitive functioning for both adults and children with end-stage kidney disease [16]. Such clinical changes are moderate to large and appear to be directly related to kidney transplantation with documented biological changes in brain functioning, indicative of causality. Delayed transplantation in children is associated with greater cognitive disability, indicating the need to offer transplantation early among children to maximize social, educational, and vocational opportunities [53].

Longer Hours or Frequent Hemodialysis

Frequent or longer hours hemodialysis may facilitate greater clearance of uremic toxins, but there is a growing body of evidence indicating that hemodialysis may have deleterious effects on the brain, particularly because of cerebral ischemia and intradialytic hypotension. In the Frequent Hemodialysis Network (FHN) trials, there was no evidence that frequent (six times weekly) hemodialysis changed the cognitive subscale of the Beck Depression Inventory compared with conventional (three times weekly) facility hemodialysis [54]. In a nonrandomized longitudinal cohort study, there was no evidence of an association of cognitive dysfunction with hemodialysis compared with peritoneal dialysis after adjustment for potentially confounding factors [55], while in a second study, patients treated with peritoneal dialysis had higher cognitive function at 1 year [56].

Anemia Treatment

Although anemia may be associated with greater white matter change in people with chronic kidney disease, to date there is no high-quality evidence that anemia correction alters neurocognitive functioning [57].

Patient and Caregiver Needs and Preferences

Reporting of patient experiences, needs, and preferences related to neurocognitive function in the context of chronic kidney disease is limited. This information is

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needed to offer insights into the level of distress experienced by patients and caregivers and their perspectives on treatment preferences that can shape the future research priorities on cognitive dysfunction. In an editorial written by a patient who had experienced end-stage kidney disease since the age of 12, she spoke of being home schooled to maximize her schooling opportunities and described how teachers and administrators did not have high expectations for her survival, leading to low motivation "to help me succeed." She advocated for interventions to support positive outcomes of children and adolescents with chronic kidney disease to manage low cognition and information retention, and the loneliness of being different to peers [58]. Adult patients report being too sick to make sense of the information they have been given about treatment options for advanced kidney disease "The doctor might have mentioned it [continuous ambulatory peritoneal dialysis] but I was so sick at the time I didn't catch on to it." Often clinicians increase decisional burden on patients as their kidney function decreases and hence when their cognitive functioning may be more impaired [59]. The experience of caregivers for adults treated with hemodialysis is one of "progressive exhaustion," accentuated by psychological and behavioral changes experienced by patients [60]. Direct qualitative research evaluating patient and caregiver experiences of cognitive dysfunction is limited. Patient experiences of information provision about kidney transplantation correlate with a substantially higher likelihood of listing for kidney transplantation, suggesting that patient information processing is important to ensure access to optimal treatments in end-stage kidney disease [61].

Conclusions

In conclusion, neurocognitive disorders are common and variable among children and adults with all stages of chronic kidney disease. Neurocognitive disorders are characterized by white matter cerebral changes and are linked to cerebral microvascular pathology. For children, cognitive disorders are linked to worse educational and social outcomes, and become more entrenched with delays to kidney transplantation. Among adults, neurocognitive disorders may fail to be recognized and impair reasoning, executive functioning, information processing, and decision-making. Adults treated with dialysis are likely to be worst affected, while transplantation provides important but incomplete resolution. Adults with neurocognitive disorders may be less likely to choose self-care dialysis due to impaired information retention. Treatments to support educational, social, and independent functioning for children and adults and their informal caregivers affected by neurocognitive disorders are absent.

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76

Pruritus

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Introduction

Pruritus attributable to kidney dysfunction, or uremic pruritus (UP), is a common and distressing symptom that affects patients with chronic kidney disease (CKD). Multiple studies imply that nephrologists underestimate the prevalence of pruritus among their patients with end-stage kidney disease (ESKD) [1–4]. When identified, many clinicians are unaware of the effective treatments available for UP, while generally ineffective therapies (e.g. antihistamines) are among the most prescribed treatments [1, 4]. Determining the causes, effective treatments, and preventative measures for UP was found by a steering committee of patients, caregivers, researchers, and clinicians in 2014 to be among the top 10 research priorities for kidney disease [5]. Despite this, many obstacles to its effective identification and management remain.

This chapter reviews the available evidence surrounding the symptom of pruritus as it affects patients with CKD. It outlines the epidemiologic data reported worldwide, describes what is known regarding the pathogenesis of UP, and outlines its clinical presentation, diagnosis, assessment tools, and available treatment options. The available studies on the treatment of UP are generally limited in quality and size but do allow for the proposal of a rational approach to diagnosis and management.

Epidemiology

Pruritus is common in patients with progressive CKD. The most comprehensive epidemiologic data on UP come from the Dialysis Outcomes and Practice Patterns Study (DOPPS) [4, 6], a large-scale observational study of over 35 000 hemodialysis patients compiled from 21 countries over the past 20 years. The most recent data from DOPPS-5, collected from 7629 patients from 17 countries in 2012 to 2015, reported a prevalence of moderate-to-extreme pruritus of 37% [4].

In addition to the DOPPS data, another 46 studies available via PubMed from over 20 countries from 1973 to 2018 reported the incidence of pruritus in ESKD patients; these data pooled together include another 11 032 total independent dialysis patients, with a mean weighted prevalence of pruritus of 50.5% [7–52]. Similarly, a meta-analysis by Hu et al. [53] compiled 42 studies published between 1988 and 2016 of 11 800 dialysis patients (including 17 studies and 3447 patients from China or Taiwan) and yielded a cross-sectional prevalence of pruritus of 55%, which is virtually the same prevalence reported in a systematic review of English-language studies by Murtagh et al. in 2007 [54].

Severity of pruritus is variably measured as further outlined below. Of the above prevalence studies, 19 included an assessment of severity of pruritus, including DOPPS [4] (Figure 76.1). If you pool the other 18 studies, the prevalence of moderate-to-severe and severe pruritus is 37.1 and 17.8%, respectively, among 6489 dialysis patients [18–35].

The prevalence of UP in ESKD patients has declined significantly over the past half century since the advent of dialysis [55], presumably related to improvements in dialysis modalities, access, and adequacy. Over the past two decades, however, the rate of decline has abated somewhat, with prevalence continuing to decrease only very slowly [4, 6, 56] (Figure 76.1).

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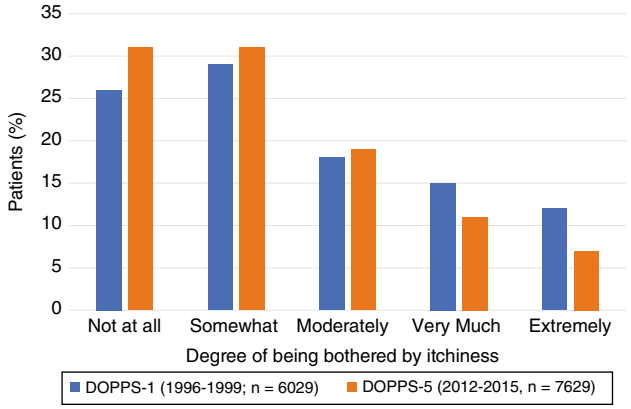

Figure 76.1 Prevalence and severity of uremic pruritus in hemodialysis patients in developed nations worldwide, 1996 to 2015. Question wording: "To what extent were you bothered by itchy skin during the past 4 weeks?" Data are from phases 1 and 5 of the Dialysis Outcomes and Practice Patterns Study (DOPPS). Overall, the percentage of hemodialysis patients being moderately, very, or extremely bothered by pruritus decreased somewhat from 45% to 37% between DOPPS-1 in 1996 to 1999 and DOPPS-5 in 2012 to 2015. DOPPS-1 data were compiled from 288 dialysis units in France, Germany, Japan, Spain, the UK, and the United States. DOPPS-5 data were compiled from 337 sites in Bahrain, Belgium, Canada, Germany, Italy, Japan, Kuwait, Oman, Qatar, Russia, Saudi Arabia, Spain, Sweden, Turkey, the UK, the United Arab Emirates, and the United States. Created using data from Pisoni et al. [6] and Rayner et al. [4].

Prevalence appears to vary significantly by geographical region and, within a given region, from center to center. DOPPS-5 reported a prevalence of moderate-to-extreme pruritus that ranged from as low as 26% in Germany to as high as 48% in the U.K [4]. Prior DOPPS reports reported a range between facilities of UP prevalence of 5–75% across nations and of 20–70% within Japan [6, 56].

The prevalence of UP in less developed countries has been far less studied but appears to be similar. Five studies from Burkina Faso, Cameroon, Nepal, and Nigeria published since 2008 collectively reported an incidence of pruritus of 37.3% among 351 dialysis patients [44–48].

Relatively few studies include data on the prevalence of UP in both patients on hemodialysis and those on peritoneal dialysis (PD). Comparisons are limited by variability in study size, measures of pruritus, and dialysis adequacy. The data overall are quite mixed. While some studies report higher rates or severity of UP in hemodialysis patients [8, 11] and others report higher rates in PD patients [35–37], the majority report rates of pruritus that are similar or statistically the same [13–18, 53]. Interestingly, only two observational studies have been carried out to explicitly compare UP rates in hemodialysis and PD; both were published in 2016, included several hundred patients, and adjusted for confounding factors, but came to opposite conclusions [11, 36].

The prevalence of UP in patients with CKD not requiring or not electing to undergo dialysis is not well reported, but it appears to be common. In a study of 49 ESKD patients managed without dialysis whose symptoms were analyzed in the month preceding death, pruritus, with a prevalence of 74%, was the second most common of 39 symptoms assessed and was very distressing in 32% [57]. However, it is not clear that conservative kidney management of ESKD results in more severe pruritus. In a study in Hong Kong of 45 ESKD patients managed with nondialytic palliative care services and 134 managed with dialysis, pruritus was the third most common and the sixth most intense out of 23 ESKD-related symptoms; however, the nondialytic group had statistically lower pruritus intensity and a nonsignificant trend toward lower pruritus prevalence (57.8% vs. 65.7%) [58]. The finding that dialysis may not reduce the prevalence of pruritus among ESKD patients has been reproduced in several other studies [18, 46–51].

The largest study of pruritus in exclusively predialysis CKD patients was published in 2016 by Solak et al. in Turkey [59]. Among 402 patients with CKD stages 2–5, including 83% stages 3–4, the prevalence of UP was 18.9% [59]. When pooling the available predialysis CKD data, the weighted mean prevalence of pruritus is 24.0% among 804 patients [46–51, 59].

Data on pruritus after renal transplant are limited. Some reviews report that pruritus is uncommon after transplant, even in those with recurrent CKD [55, 60], citing data from 1982 that only 2% of post-transplant patients experience pruritus [40]. However, modern studies report the prevalence of pruritus indeed decreases substantially (by roughly half) after renal transplantation, but it remains significant at 25–38% [61, 62].

Similarly, data about UP in children are limited. A 1999 study of 199 children in Germany reported that pruritus among children on dialysis is less common (9.1% vs. 18.8% prevalence) and less severe than in adult dialysis patients [55]. Another study of 30 children with advanced CKD in the United States reported incidences of pruritus closer to those reported in adults, specifically 50%, 69%, and 25% among those treated with transplant, dialysis, and conservative kidney management, respectively [63].

A variety of patient and dialysis characteristics have been associated with an increased burden of UP, including lower dialysis adequacy (i.e. Kt/V) [12, 36, 64, 65], use of certain dialysis membrane types [33, 66], viral hepatitis infection, liver disease, and/or elevated transaminases [4, 6, 11–14, 24, 56, 67], smoking [6, 56], older age [4, 6, 41, 56], male gender [6, 13, 30, 56], and underlying depression [6, 28, 29, 68]. However, multiple studies analyzing these very same factors have failed to replicate these associations and a few have yielded contrary associations, particularly with regard to Kt/V, age, and gender [4, 7, 27, 31, 33, 64].

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Clinical Significance

UP has been repeatedly demonstrated to decrease quality of life (QoL), to contribute to other symptoms, especially poor sleep, that further impair QoL, to be associated with depression, and to be an independent predictor of poor outcomes, including mortality [6, 10, 17, 28–32, 39, 46, 56, 68–70].

In specifically the DOPPS-1 and -2 cohorts (1996–2004, $n = 18\,801$), dialysis patients with moderate-to-extreme pruritus were statistically more likely to feel drained, have poor sleep quality, and be diagnosed with depression [6]. Those with extreme pruritus had physical and mental QoL scores 15–20% lower than patients without pruritus [6]. They also found a 17% increase in mortality associated with moderate-to-extreme UP, but this difference was no longer statistically significant when adjusting for sleep quality [6]. The associations between UP and feeling more drained, poorer sleep quality, increased rate of depression, lower physical and mental QoL scores, and increased mortality were replicated in the Japanese DOPPS-3 cohort (1996–2008, $n = 6480$), with the exception that the mortality relationship persisted even after adjustment [56]. The independent association between moderate-to-severe UP and mortality was replicated in a prospective multivariate survival analysis of 321 chronic hemodialysis patients in Taiwan [26]. In a cross-sectional study of 980 hemodialysis patients in Brazil, patients with severe pruritus had a 25% decrease in kidney disease burden-related QoL, a decrease driven primarily by sleep disturbance, depressive symptoms, and dry skin [32]. Another study of US hemodialysis patients by Mathur et al. also reported a statistically significant impact of UP on QoL and on mood, social relations, and sleep; they noted that a decrease in intensity of UP of 20% was sufficient to produce a significant improvement in QoL [10]. Similar findings have been reproduced in Germany, Italy, Poland, and the UK [17, 28, 39, 69]. Yamamoto et al. followed the Japanese DOPPS cohort longitudinally and showed, interestingly, that baseline depressive symptoms predicted the subsequent development of severe pruritus in hemodialysis patients [68].

Limited data have also demonstrated a statistically significant impact of pruritus on QoL in both renal transplant recipients [61, 62] and predialysis CKD patients [46].

Clinical Presentation

The clinical presentation of pruritus in CKD varies greatly from patient to patient. Prospective observational longitudinal studies of hemodialysis patients in both the United States ($n = 103$) [10] and Germany ($n = 860$) [31, 70] have detailed a variety of the clinical aspects of UP. The majority of patients have itching daily or nearly daily [10, 31, 70]. Most patients have itching that affects large, discontinuous but bilateral and symmetric areas of skin [10]. Itching generally is worse at night than during the day [10, 13, 70]. Interestingly, in the German cohort, over 50% of the patients described their UP with terms suggestive of a neuropathic process, such as "tingling, sharp, burning and painful" [70]. The affected areas most commonly include the back, arms, legs, and scalp [13, 31, 70] and may remain constant or migrate over time [10]. Precipitating or aggravating factors vary significantly among patients but commonly include heat, dialysis, stress, cold, physical activity, showering, and rest or sleep [13, 38, 39, 70]. Unfortunately, most affected patients will continue to have the pruritus for months to years [10, 31, 70].

On examination, apart from near-universal xerosis, many patients with UP will have normal skin. However, others may have secondary cutaneous phenomena such as pigment changes, excoriations, nodule formation (i.e. prurigo nodularis), skin thickening (i.e. lichenification), and less commonly perforating or blistering lesions such as acquired perforating dermatosis or pseudoporphyria (Figure 76.2) [8, 18–20, 45, 47–50, 70–72]. However, in patients with abnormal appearing skin, nonuremic causes of pruritus must be considered.

Indeed, as the presentation of UP can be variable, it may be difficult to differentiate it from other causes of itch. A nonuremic cause for pruritus should generally be considered in patients who are refractory to a reasonable trial of treatment, whose symptoms are largely asymmetric, with bullous or ulcerating lesions, or with clinical findings characteristic of other systemic diseases. Additionally, pruritus may manifest as a reaction from recently initiated or long-standing drug. Table 76.1 outlines a differential diagnosis of nonuremic and treatable causes of itch in patients with CKD [74].

Pathophysiology

The pathophysiology underlying pruritus in general has been increasingly elucidated over the last few decades, though much remains to be explained. The first neuron type found to transmit itch was the histamine-dependent slowly conducting unmyelinated C-fiber, but a variety of nonhistaminergic neurons have subsequently been discovered that are likely also involved in the neural pathways that produce itch, which may account for the common clinical finding of pruritus being unresponsive to antihistamines [75, 76].

UP has been less extensively studied than pruritus in general and may be caused by mechanisms different than those underpinning pruritus from other etiologies. Five

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Figure 76.2 Typical skin changes observed in patients suffering from uremic pruritus. (a) Scratch marks with excoriations at the lower leg. (b) Prurigo nodularis: typical hyperkeratotic partly excoriated nodules located on the forearm. (c) Deep scars and prurigo nodules on the shoulders and back of a female patient. (d) Acquired perforating dermatosis: multiple papulonodular lesions over the lower extremities with central crusting in a 45-year-old woman with ESKD. (e) Pseudoporphyria: multiple erosions associated with skin hyperpigmentation involving the dorsal aspect of the hands of a 60-year-old man with ESKD. *Source:* Reproduced with permission from Mettang and Kremer [71] and Kurban et al. [72].

abnormalities specific to CKD that have been proposed to mediate UP include (i) changes associated with hyperparathyroidism, (ii) structural skin alterations, (iii) systemic inflammation and immune dysregulation, (iv) imbalance of the endogenous opioid system, and (v) primary alterations in nociceptive sensory pathways [73, 77, 78].

The possible role of hyperparathyroidism and calcium-phosphate balance in the pathophysiology of UP was first proposed over a half-century ago [79]. Though data to support this theory are limited at best, per the most recent DOPPS-5 data most practicing nephrologists worldwide still believe phosphorus control to be the most important

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Table 76.1 Nonuremic causes of itch.

Primary dermatologic conditions	Systemic conditions
1) Drug-induced hypersensitivity and other allergies 2) Contact dermatitis 3) Psoriasis 4) Xerosis 5) Urticaria 6) Dermatophytosis (tinea cruris, tinea pedis, tinea corporis) 7) Bullous pemphigoid 8) Kyrle disease (acquired perforating dermatitis) 9) Lichen simplex chronicus 10) Infestations • Bed bugs • Scabies • Lice	1) Hypercalcemic states 2) Cholestasis • Viral hepatitis • Primary biliary cirrhosis • Drug-induced cholestasis 3) Hematologic malignancy • Hodgkin's lymphoma • Cutaneous T-cell lymphoma • Polycythemia vera • Multiple myeloma • Solid tumors with paraneoplastic syndrome 4) Postherpetic neuralgia 5) Human immunodeficiency virus 6) Hypothyroidism 7) Iron deficiency

Source: Adapted with permission from Combs et al. [73].

factor in treating pruritus in ESKD [4]. While multiple observational studies have revealed associations between UP and higher serum calcium, phosphorus, and/or calcium-phosphorus product [6, 9, 11, 27, 30, 35, 56, 64, 66, 80] or serum parathyroid hormone (PTH) [9, 14, 19, 29, 30, 56, 66], these findings have not been replicated consistently [4, 7, 8, 10, 12, 13, 16, 17, 22–24, 32, 34, 36, 37, 41, 42, 59, 65, 81]. For example, DOPPS-5, the largest observational cohort of UP currently available, failed to reveal any statistically significant correlation between pruritus and calcium, phosphorus, their product, or PTH levels [4]. A direct role of PTH on the skin appears unlikely as intradermal injection of human PTH fragments elicits no cutaneous response and PTH itself is not present in the skin of ESKD patients with UP [82]. Limited data also suggest that UP does not correlate with the presence of radiographic renal osteodystrophy [80]. However, the role of mineral metabolism in UP may be more complex than can be appreciated from serum analyses alone. For example, small studies have demonstrated increased deposition of calcium and phosphorus in the skin tissue of ESKD patients with UP [83, 84].

Multiple studies have found UP to be associated with xerosis (dry skin) [20, 31–35, 43, 50, 59, 70], which specifically correlates to reduced stratum corneum hydration in ESKD patients with UP [35]. The possible pathogenic role of xerosis in UP is implied by some evidence that improving skin hydration can ameliorate UP [35, 85]. However, some patients with severe xerosis do not have pruritus, suggesting that it is more likely to be an aggravating rather than a principal causative factor [71]. Other skin changes documented in patients with ESKD that may play a role in UP include abnormal skin pH, reduced sebum and sweat excretion, sweat gland atrophy, and impaired skin perfusion during hemodialysis [86–88]; however, the data linking these abnormalities specifically to UP are limited and inconsistent [88].

An increasing body of evidence links UP to inflammation. Multiple reports, including DOPPS-5, have found UP to be associated with increased serum C-reactive protein [4, 7, 12, 24, 26, 42, 89] and depressed serum albumin [4, 6, 36, 90, 91], the latter having been proposed to be primarily a marker of inflammation in ESKD [92]. Furthermore, patients with UP have been shown to have elevated serum levels of interleukin-2 [93], interleukin-6 [89], and interleukin-31 [12], three proinflammatory cytokines that have been implicated as mediators of pruritus from psoriasis and other dermatologic diseases [94–96]. A variety of other inflammatory mediators, such as the neuropeptide substance P (the proposed target of capsaicin) [97] and various proteases [98], may also be involved in UP, although data to support their roles remain limited or inconsistent [14, 71, 74, 99].

Investigation of the possible role of opioid receptors in pruritus stems from the common clinical observation that mu-receptor agonists, especially if given by the epidural or spinal route, can cause or worsen pruritus [99]. A series of animal studies has further elucidated the role of central opioid receptors in mediating pruritus, including histamine-independent pruritus mediated by substance P [100–102].

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Whereas central mu-receptor agonism enhances pruritus induced by substance P or histamine, central kappa-receptor agonism inhibits this effect (Figure 76.3) [100–102]. Contrary to the antipruritic effect of scratching (i.e. pain), the pruritus induced by mu-opioid agonists is felt to be mediated by disinhibition of a central itch response associated with their antinociceptive properties [103]. The importance of this opioid system in UP is suggested by several studies showing that serum levels of endogenous opioids, such as beta-endorphin, are elevated in patients with ESKD [106–108] and/or increase during hemodialysis [109], though other studies have failed to replicate these findings [110, 111]. Furthermore, an increasing number of therapeutic trials, discussed below, have been carried out using opioid modulators and have shown promise.

The central role of the nervous system in mediating chronic itch (which would include UP) has been increasingly elucidated over the last few decades [76, 112]. The tendency for UP to be distributed with "striking mirror symmetry" has been proposed to be a reflection of a central or neurogenic etiology [10]. Similarly, altered itch perception is implied by a study in which histamine- and serotonin-induced skin flares in hemodialysis patients were found to be statistically smaller than in non-ESKD controls despite similar or higher perceived itch in the hemodialysis patients [113]. As previously mentioned, some patients describe their UP with neuropathic terms such as "tingling, sharp, burning, and painful" [70]. Prior immunohistochemical studies have shown patients with ESKD with or without pruritus, but not healthy controls, "sprout" small unmyelinated cutaneous nerve fibers in an abnormal distribution throughout the epidermis [114]. Clinically, UP and neuropathy and/or paresthesia have also been found to coexist in a substantial proportion of patients and to be statistically correlated [25, 115], with one study reporting that over 70% of ESKD patients with neuropathic pain, including those with electromyography-proven neuropathy, also have pruritus [116]. Finally, the efficacy of gabapentin in the treatment of UP serves as fairly compelling support for the neuropathic theory of UP [117].

The putative role of histamine in UP warrants specific discussion given antihistamines remain, even as recently as 2015, the most prescribed agents by nephrologists for UP [4]. While histamine may play some role in UP, with some proposing histamine release from mast cells as a final common pathway for the various mechanisms underpinning UP [74], data to support this remain inconsistent, with some reports showing a correlation between

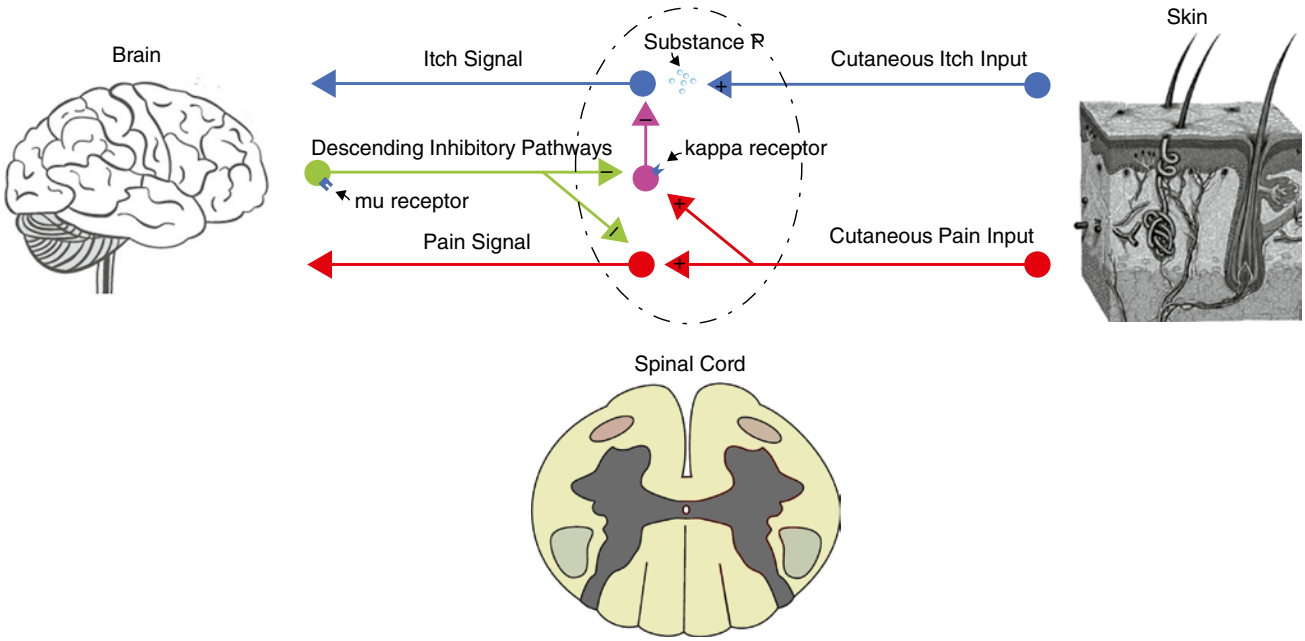

Figure 76.3 Simplified schematic of the opioid hypothesis of pruritus and of the interplay of pruritus and pain. Histamine-independent afferent cutaneous itch fibers transmit itch signal to the brain via release of neurotransmitters such as the neuropeptide substance P in the spinal cord (blue). Scratching is thought to inhibit the sensation of itch via stimulation of cutaneous pain fibers (red) which activate inhibitory interneurons (magenta) in the spinal cord. Mu-opioid receptor antagonists are thought to cause pruritus in the central nervous system via stimulation of descending inhibitory pathways (green) which, in addition to mediating (in part) their antinociceptive properties, disinhibit central itch signaling. Kappa-opioid receptor agonists, in contrast, inhibit itch signaling by binding to their receptors on inhibitory interneurons in the spinal cord. *Source:* Figure adapted with permission from Schmelz [103], incorporating content from Akiyama et al. [104] and Kardon et al. [105].

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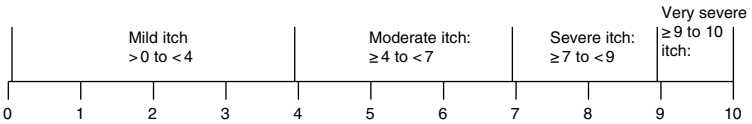
UP and plasma histamine levels and/or skin mast cell number, proliferation, or activation [51, 91, 98, 118] while others have not [16, 84, 119]. Possibly the strongest and most clinically relevant argument against a principal role for histamine in the mediation of UP, as further discussed and referenced below, is the consensus that H1 receptor antagonists are generally ineffective in the treatment of UP [120].

Evaluation

Prior to initiating treatment for pruritus, it is helpful to obtain information regarding its severity to track response to therapy. Pruritus is a symptom and is thus inherently subjective. Scratch lesions can be quantitated; however, this assessment method often fails to capture the significance of pruritus to patients. Therefore, pruritus is typically assessed via patient-reported outcomes (PROs). Because QoL, sleep disturbance, anxiety, and depression are strongly associated with pruritus intensity, these measures are often included in UP assessment tools. Several PRO scales have been validated for use in UP [121]. Monodimensional measures, such as the visual analogue scale (VAS; Figure 76.4a), address one symptom at a time with one scale and are simple and fast but are subject to confounding factors that affect QoL. Multidimensional measures, such as the ABC questionnaire [10] (Figure 76.4b), track more than one symptom, change in symptoms over time, or more than one assessment of a particular symptom, but often do not provide quantitative values and may be difficult for patients who must make unequivocal selections of a category. Table 76.2 lists several PRO scales validated for use in UP and recommendations for their use.

Treatment

Most of the published data regarding treatment of UP are either retrospective or derived from underpowered prospective studies, therefore treatment recommendations remain largely based on expert opinion. Here we outline the most common available therapies for UP and the evidence that supports them (Table 76.3).



(a)

Which of these patients are you most like? (Mark One)

Patient A:

I do not generally have scratch marks on my skin.
I do not generally have a problem sleeping because of itching.
My itching does not generally make me feel agitated or sad.

Patient B:

I sometimes have scratch marks on my skin.
I sometimes have problems sleeping because of itching.
My itching can sometimes make me feel agitated or sad.

Patient C:

I often have scratch marks on my skin that may or may not bleed or get infected.
I often have a problem sleeping because of itching.
My itching often makes me feel agitated or sad.

(b)

Figure 76.4 Examples of monodirectional (a) and multidirectional (b) patient-reported outcome (PRO) scales. (a) Visual Analogue Scale (VAS). *Source:* Adapted from Reich et al. [122]. (b) Self-Assessed Disease Severity (ABC Scale). *Source:* Adapted from Mathur et al. [10].

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Table 76.2 Symptom scales validated for use in the evaluation and treatment of uremic pruritus.

Measurements	Tools (and references)	Advantages	Disadvantages	Recommended use
Pruritus intensity (unidimensional)	Visual Analogue Scale (VAS) [123] Numerical Rating Scale (NRS) [122, 123] Verbal Rating Scale (VRS) [123]	Simple and fast	Score may reflect other nonitch factors	Routine clinical use
Pruritus intensity (multidimensional)	Itch Severity Scale [124]	Simple and fast	Patients may face difficulties in unequivocal selection of a category	Clinical trials
	Self-Assessed Disease Severity (ABC Scale) [10]	Simple and fast	Not quantitative	Routine clinical use and screening for clinical trials
	Brief Itching Inventory [10]	Assesses quality of life and dermographic distribution	Not quantitative	Clinical trials
	Skindex-10 [10]	Assesses quality of life	Not quantitative	Clinical trials
	Itch MOS (Medical Outcomes Study) [10]	Assesses sleep disturbance		Clinical trials
Pruritus course	5-D questionnaire [125]	Comprehensive	Not yet conclusively validated	Clinical trials
Tracking response to treatment	Patient Benefit Index for pruritus (PBI-P) [126]	Assesses response to treatment	Longer survey (27 variables); harder to use systematically in routine clinical care	Especially useful for setting patient-specific therapy goals

Source: Adapted with permission from Combs et al. [73].

Topical Treatments

As discussed, xerosis is found in most patients with ESKD and frequently aggravates pruritus. Skin hydration with aqueous cream emollient [35] and baby oil [127, 128] have both been demonstrated to effectively reduce skin dryness and severity of UP and improve patient QoL when applied two to four times daily. Given the benign side effect profile of emollients and the burden of xerosis in patients with ESKD, the cornerstone of UP therapy is adequate skin hydration.

In addition to pure emollients, other topical agents have been used with some success to treat pruritus (Table 76.3). For example, several small placebo-controlled trials have demonstrated symptom relief with 0.025–0.03% capsaicin ointment applied two to four times daily to affected areas [129–131]. Capsaicin was generally well tolerated apart from initial burning on application and, as such, is presumed to be more useful in patients with localized rather than generalized pruritus [129–131]. Similarly, 1% pramoxine hydrochloride lotion was tested in a single-center randomized double-blind study of hemodialysis patients and demonstrated statistically significant effectiveness when applied twice daily for 4 weeks [132].

Tacrolimus, formulated as a 0.1% or 0.03% ointment (Protopic, Astellas Pharma US, Inc.), is a topical immunomodulating agent that has been approved for the treatment of atopic dermatitis. Its use in treating UP has been tested in a few small single-center studies with conflicting results [134–136]. Additionally, in response to case reports and animal studies reporting rare associated malignancies such as lymphoma and skin cancer, the United States Food and Drug Administration (FDA) issued a black box warning in 2005 for tacrolimus ointment and recommended that its use be limited to those who have failed other therapies and to treatment periods of less than 6 weeks. However, as discussed, most patients with UP are affected for months to years [10, 31, 70].

Systemic Treatments

Of all the systemic therapies currently used for treatment of UP, gabapentinoids have most consistently demonstrated success in small clinical trials. Recently Simonsen et al. published a systematic review of UP treatments and found nine studies of adequate quality evaluating gabapentin or pregabalin; they concluded that, though long-term data are lacking, there was an overall statistically

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Table 76.3 Summary of evidence: treatment of uremic pruritus.

Treatment (and references)	Recommended dose in ESKD	Recommendation	Common side effects/toxicity	Certainty of evidence (GRADE)	Strength of recommendation
Topical					
Emollients [35, 127, 128]	Apply 2–4 times daily	We suggest routine use in all patients with uremic pruritus, particularly in those with dry skin	Minimal	Very low	Weak
Capsaicin [129–131]	Apply 0.025–0.03% ointment 2–4 times daily	We suggest a trial of capsaicin be used on affected areas in those with localized uremic pruritus	Local skin burning, stinging, or redness	Low	Weak
Pramoxine [132]	Apply 2–4 times daily	We suggest pramoxine be considered as alternative topical therapy prior to systemic treatment	Minimal	Low	Weak
Gamma-linolenic acid [133]	Apply four times daily	We suggest gamma-linoleic acid be considered as alternative topical therapy prior to systemic treatment	Minimal	Low	Weak
Tacrolimus ointment (Protopic) [134–136]	N/A	We suggest tacrolimus ointment not be used in patients with UP	Skin warming; FDA black box warning (concern for malignancy)	Very low	Weak
Pharmaceutical					
Gabapentin [117, 137–141]	100–300 mg PO thrice weekly after HD; 100–300 mg PO qHS in PD[a]; 100 mg PO every other night to 300 mg PO qHS in CKD5-CKM	We suggest a trial of gabapentin be used, starting at lowest dose, for generalized UP not responding to topical therapy	Somnolence, dizziness, drowsiness, loss of balance, tremulousness, risk of misuse	Low to moderate	Weak
Pregabalin [116, 142–144]	25–75 mg PO thrice weekly after HD; 25–75 mg PO qHS in PD[a]; 25 mg every other night to 75 mg qHS in CKD5-CKM	We suggest a trial of pregabalin be used, starting at lowest dose, for generalized UP if not responding to or intolerant of gabapentin	Somnolence, dizziness, drowsiness, loss of balance, tremulousness, risk of misuse	Low	Weak

(*Continued*)

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Table 76.3 (Continued)

Treatment (and references)	Recommended dose in ESKD	Recommendation	Common side effects/toxicity	Certainty of evidence (GRADE)	Strength of recommendation
Antihistamines [38, 73, 97, 113, 120, 145–149]	N/A	We suggest antihistamines not be used for UP	Anticholinergic side effects, confusion, sedation	Low	Weak
Naltrexone [37, 150]	N/A	We suggest naltrexone not be used in patients with UP	Stomach upset	Very low	Weak
Nalfurafine [151, 152]	5 μg PO daily or 5 μg IV thrice weekly after HD	Consider, if available[b], for those who fail trial of gabapentinoids	Insomnia, constipation, nausea, somnolence	Low	Weak
Nonpharmaceutical					
UVB phototherapy [153–157]	Variable	We suggest UVB phototherapy be used as second- or third-line therapy in refractory severe UP	Sunburn, tanning; possible increased risk of skin cancer (especially if immunosuppressed)	Low	Weak
Acupuncture [158]	N/A	We suggest acupuncture be considered as second- or third line therapy in interested patients with refractory severe UP	Mild pain	Very low	Weak
Dialysis prescription modification [12, 36, 64, 65, 117, 159]	N/A	We suggest high-flux HD and adequate dialysis adequacy as treatment for UP	N/A	Low	Weak

CKD5-CKM, stage 5 chronic kidney disease treated with conservative kidney management; ESKD, end-stage kidney disease; HD, hemodialysis; IV, intravenous; KDIGO, Kidney Disease: Improving Global Outcomes; KDOQI, Kidney Disease Outcomes Quality Initiative; N/A, not applicable; PD, peritoneal dialysis; PO, by mouth; qHS, nightly; UP, uremic pruritus.
[a] No data available specific to treatment of UP in setting of PD; suggested doses provided are derived from use in other settings.
[b] Currently not available except for in Japan.

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significant benefit of gabapentinoids versus placebo [117]. More specifically, Nofal et al. studied 54 hemodialysis patients with pruritus and measured the efficacy of gabapentin versus placebo for 1 month. Gabapentin was initiated at 100 mg thrice weekly after dialysis and titrated up to a maximum of 300 mg thrice weekly, and 88.4% of treated patients had a 50% or more decrease in VAS score versus 22.2% of placebo patients [137]. Cheikh Hassan et al. published a single-center retrospective cohort study testing the use of gabapentin for the treatment of pruritus in CKD ranging from stage 3 to ESKD [138]. Gabapentin successfully reduced pruritus with a median daily dose of 100 mg; 14% of hemodialysis patients and 47% of nondialysis patients experienced one or more side effects, leading to a 17% discontinuation rate in the nondialysis group [138]. Gunal et al. enrolled 25 hemodialysis patients in a randomized placebo-controlled, double-blind trial of gabapentin at 300 mg thrice weekly after dialysis for 4 weeks and reported a significant decrease in mean VAS score from 7.9 to 1.2, with no dropout secondary to side effects [139]. Other small-scaled studies have demonstrated similar improvement in pruritus with similar doses of gabapentin following hemodialysis [140, 141]. Pregabalin (Lyrica, Pfizer, Inc.) has been demonstrated to be similarly effective for the treatment of UP [116, 142–144].

Many providers reasonably worry about the safety of gabapentinoids in patients, especially older patients, with kidney dysfunction. In the setting of the North American opioid epidemic, concern for misuse or abuse of gabapentinoids is also increasing. In 2016, gabapentin was the tenth most commonly prescribed medication in the United States while pregabalin ranked eighth highest in drug spending [160]. Patients are increasingly taking higher-than-recommended doses of gabapentinoids to achieve euphoric highs, and gabapentinoids are increasingly being identified in post-mortem toxicology analyses [161]. Possible risk factors for gabapentinoid abuse include current or prior substance abuse (particularly of opioids and benzodiazepines) and other underlying psychiatric comorbidities [161]. Specific to ESKD, a recent analysis of United States Renal Data System data revealed that 19% of US hemodialysis patients received gabapentin, of whom 43% received it at inappropriate doses (greater than 300 mg) [162]. Gabapentin use at these higher doses was associated with 50, 55, and 38% higher hazards of altered mental status, fall, and fracture, respectively [162]. Rather than avoiding gabapentinoids when indicated, we recommend that providers caution patients about the risks of taking medications beyond how they are prescribed, particularly in those at high risk for misuse, and to ensure that dosing is appropriate for each patient's kidney function, comorbidities, and frailty.

As mentioned above, a variety of studies have investigated opioid receptor modulators for the treatment of UP. Naltrexone (naltrexone hydrochloride, Teva Pharmaceuticals USA, Inc.), an oral mu-opioid receptor antagonist, was tested in two studies of the treatment of UP in ESKD at a dose of 50 mg daily; while the first study showed benefit, a subsequent larger and longer-term study did not [37, 150].

Nalfurafine (Remitch, Toray Industries, Inc.), a kappa-opioid receptor agonist, has been tested in oral and intravenous form in the treatment of UP. In an open-label single-arm prospective trial of 211 hemodialysis patients treated for 52 weeks with 5 μg of oral nalfurafine daily, 145 patients completed the study and experienced a significant decrease in mean VAS score from 75.2 to 30.9 at study termination [151]. The authors reported no evidence of drug dependence during the trial, though 48.8% of patients had adverse reactions, including insomnia (19.4%) and constipation (7.1%) [151]. At study termination, treatment effects of the medication appeared to rapidly reverse, but the subjects were not followed long enough to determine if VAS scores returned to baseline [151]. Similarly, Wikstrom et al. reported a statistically significant effect in two randomized, double-blind placebo-controlled trials of 144 hemodialysis patients with UP who received 5 μg of intravenous nalfurafine thrice weekly after dialysis for 4 weeks [152].

Nalbuphine ER (Trevi Therapeutics, Inc.) is an oral extended-release dual mu-opioid antagonist and kappa-opioid agonist currently under investigation for the treatment of UP. A recently published phase 2/3 double-blind, randomized, placebo-controlled trial in 47 sites in the United States, Romania, and Poland assigned 371 patients in a 1 : 1 : 1 ratio to placebo, nalbuphine 60 mg twice daily, or nalbuphine 120 mg twice daily for 6 weeks, with a primary outcome of change in numerical rating scale (NRS) scores [163]. The dose of 120 mg twice daily of nalbuphine produced a statistically significant benefit versus placebo with mean change in NRS of 3.5 versus 2.8 [163]. The authors reported "no adverse safety trends other than expected from a centrally acting agonist–antagonist opioid drug class" [163].

Cara Therapeutics, Inc. developed CR845, a "potent peripheral kappa-opioid receptor agonist," for the treatment of UP and presented preliminary results in a 2017 abstract [164]. The phase 2, double-blind randomized placebo-controlled study enrolled 174 hemodialysis patients with moderate-to-severe pruritus in the US and they received intravenous bolus placebo or CR845 at doses of 0.5, 1.0, or 1.5 μg/kg thrice weekly for 8 weeks. The dose of 0.5 μg/kg produced a statistically significant change versus placebo in their primary outcome, mean change in NRS at week 8 from baseline ($P < 0.001$). They

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reported that this reduction in itch was associated with a "substantial improvement in multiple measures of itch-related QoL" and that CR845 was "well-tolerated." A phase 3 trial is now underway, and Cara Therapeutics was granted breakthrough designation for CR845 by the FDA in June 2017.

Finally, as previously noted, antihistamines are commonly used to treat UP. However, a few studies and a larger number of reviews all point to their general lack of efficacy in treating UP, with several reviews speculating that any perceived benefit seen with antihistamines is due to sedation rather than a true antipruritic effect [38, 73, 97, 113, 120, 145–149]. One small study specifically suggested that antihistamines are no more effective than emollients [38]. Another small study documented that the ability of antihistamines to prevent pruritus, which can be reproduced experimentally in normal patients, is specifically lost in patients with UP [113]. Furthermore, given the risk of side effects, such as confusion, sedation, and anticholinergic toxicity, particularly in an ESKD population that often is older with multiple comorbidities, antihistamines are generally not recommended as first- or second-line therapies for UP.

Hemodialysis Prescription Modification

There is a paucity of high-quality prospective data aimed at determining the effects of changing dialysis adequacy, modality, duration, or other measures on symptoms of pruritus. The limited prospective interventional [117, 159] and observational [64] data available generally support the use of high-flux hemodialysis, which is now the standard of care in most developed countries.

Phototherapy

In the late 1970s, Gilchrest et al. published several small studies of patients with CKD that demonstrated success of type B ultraviolet light (UVB) therapy in the treatment of UP, noting that some patients had generalized improvement in symptoms even when only part of the affected body parts were treated [153–155]. Tan et al. published a meta-analysis of randomized controlled trials of UP treatments in 1991 and identified UVB phototherapy as the only treatment available at the time that successfully fulfilled the criteria for clinical significance [156]. However, the most recent randomized controlled trial testing UVB therapy efficacy, published in 2011, did not demonstrate significant benefit [157]. Much is still unknown about the long-term effects of UVB therapy and its use should be carefully considered prior to initiation, particularly in patients who are immunosuppressed or in those who may soon undergo renal transplantation.

Acupuncture

Acupuncture is commonly used worldwide as a primary, adjunct, or alternative treatment for pain and other symptoms. Kim et al. published a meta-analysis of prospective clinical studies of needle acupuncture for UP in patients with ESKD and concluded that, despite six separate trials reporting the beneficial effects of acupuncture, most of the trials demonstrated high risk of bias and therefore current evidence is insufficient to support its efficacy [158]. However, acupuncture has virtually no lasting side effects and therefore could be very reasonably offered as an alternative therapy to interested patients with UP who do not respond to first-line treatments, who are unwilling to take systemic medications, or who have a particular interest in acupuncture.

Approach to Therapy

There are no formal published guidelines regarding the treatment of UP; however many reviews have published treatment recommendations [71, 77]. We recommend taking a stepwise approach to the treatment of UP, beginning with addressing contributing factors such as skin hydration, optimization of dialysis adequacy, and patient education on the importance of avoiding or minimizing scratching and the use of drying soaps. If symptoms persist, providers may offer pharmacologic or nonpharmacologic therapy starting with topical therapies, given lower risk of toxicity, before progressing to systemic treatments (Figure 76.5). Providers should approach treatment according to patient preference and with consideration of available resources, of potential drug–drug interactions and adverse drug reactions, and of their own comfort level in prescribing the various therapies.

Conclusion

UP is a common, often distressing, and yet frequently underrecognized symptom in patients with progressive CKD. UP itself and its associated symptoms significantly impair QoL. UP can present variably, but tends to affect large, discontinuous but symmetric areas of skin. A variety of alternative systemic or dermatologic conditions should be considered in the differential diagnosis of itch in patients with CKD, especially those with atypical features. The pathogenesis of UP remains poorly understood. There are likely multiple, coexisting mechanisms involved, beyond abnormal serum biochemistry, which does not appear to be a major driver of UP in the current era of dialysis. Available treatments for UP are suboptimal. Management of UP should focus initially on aggressive

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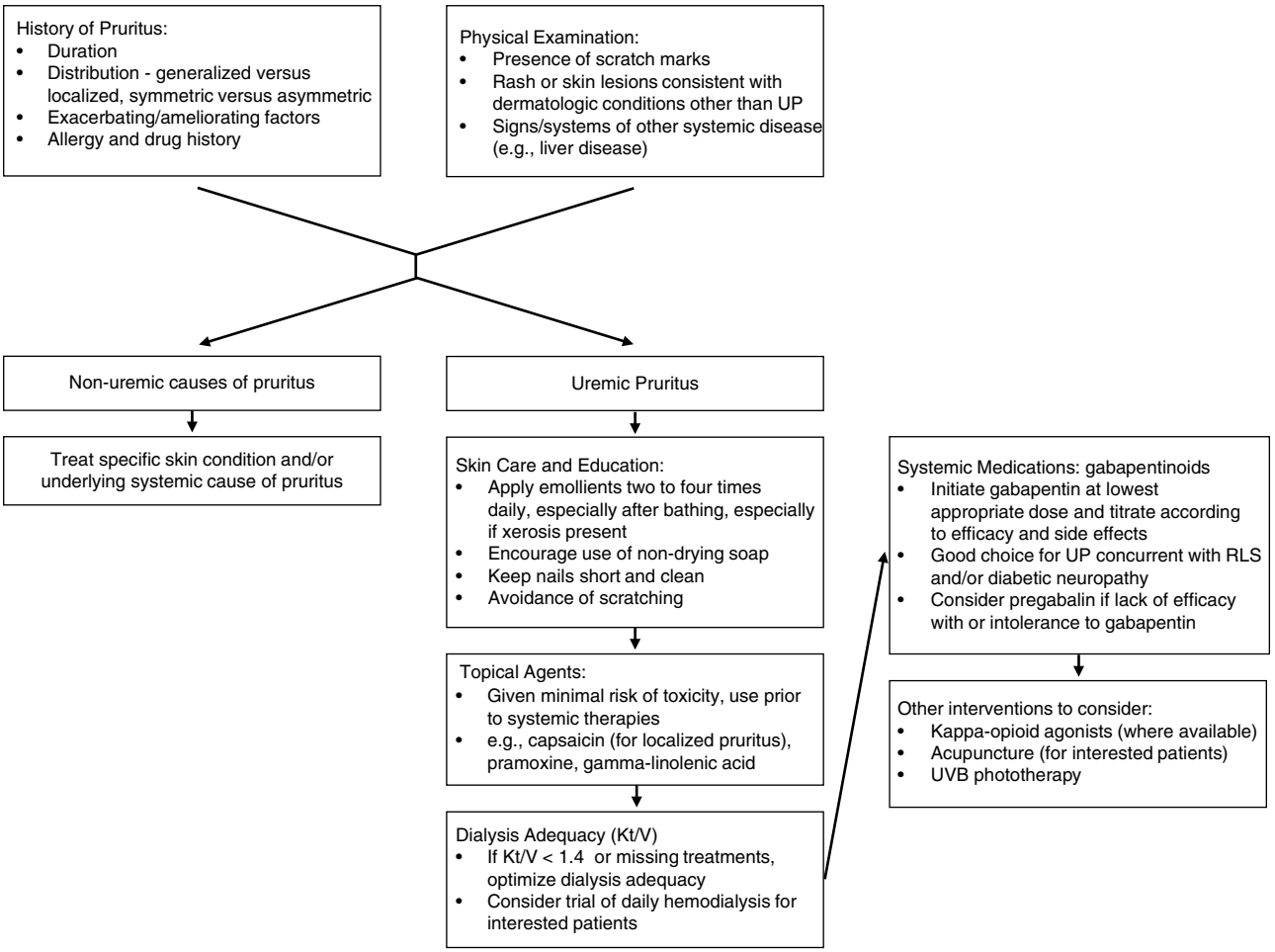

Figure 76.5 Step-by-step approach to the treatment of uremic pruritus. See Table 76.3 for further treatment details including dosing recommendations. UP, uremic pruritus; RLS, restless leg syndrome; UVB, type B ultraviolet light.

skin hydration, avoidance of drying soaps, and patient education on skincare, including minimization of scratching, before considering other therapies given the limited supporting data. A better pathophysiologic understanding of UP is needed for the development of more effective preventive and management strategies.

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77

Sexual Dysfunction

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Introduction

Sexual dysfunction may be frequently experienced by patients who have chronic kidney disease (CKD) as measured by specific tools, although the impact of any sexual dysfunction on patients' lives and relationships may be less than previously understood [1]. The *Diagnostic and Statistical Manual of Mental Disorders 5* (DSM-5) classifies several distinct types of sexual dysfunction for men and women that have been present for at least 6 months and cause significant distress [2]. For men, these include erectile disorder, male hypoactive sexual desire disorder, delayed ejaculation, substance/medication induced sexual dysfunction, and other/unspecified sexual dysfunction. For women, these are female sexual interest/arousal disorder, genito-pelvic pain/penetration disorder, substance/medication induced sexual dysfunction, and other/unspecified sexual dysfunction.

Most information about sexual dysfunction is available for patients with CKD treated with dialysis or transplantation, while studies among those with earlier stages of CKD are infrequent [3]. The prevalence of sexual dysfunction is also challenging as existing measurement scales classify sexual inactivity as dysfunction and cannot completely capture the level of distress that patients may or may not experience in association with specific symptoms. For example, sexual difficulty in the presence of CKD has been reported in 2% of women treated with hemodialysis [4], although the true prevalence may have been impacted by the high prevalence of sexual inactivity among this patient group, which can result in overmeasurement on standardized diagnostic tools [3]. In a Swedish study, less than 45% of women with low sexual interest perceived these experiences as distressing [5]. In a meta-analysis of 50 observational studies, approximately 70% of men reported erectile dysfunction, with increased symptomatology occurring in association with depression, older age, and diabetes [3]. For men and women after transplantation, the frequency and personal importance of sexual activity may decrease, while relationship and life satisfaction may be maintained [6].

CKD leads to altered biological secretion of hypothalamic, pituitary, and gonadal hormones which usually act to maintain sexual function, including luteinizing hormone (LH), follicle-stimulating hormone (FSH), testosterone, estrogen, prolactin, and sex hormone binding globulins. In addition, comorbidities and medications can lead to hypogonadism or erectile dysfunction, including high body mass, diabetes, vascular disease, depression, and anemia, and medications including diuretics, beta blockers, calcium-channel blockers, and methyldopa.

Evidence for treatments of sexual dysfunction among people with CKD is sparse [7]. Therapeutic approaches include treatments leading to vasodilatation (phosphodiesterase 5 inhibitor), increased sex hormone concentrations (zinc supplementation, bromocriptine, testosterone, estrogen), local therapeutic approaches to reduce erectile dysfunction (vacuum tumescence devices, penile prostheses, intracavernous injection, transurethral injection), and psychotherapeutic and psychoeducational interventions. Recent systematic reviews of trials have shown that there is often low or very low certainty that treatment of sexual dysfunction makes a difference to the outcomes that directly impact on patients, including health-related quality of life [7].

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Men and women with kidney disease are frequently sexually inactive. For men, there may be a desire for greater sexual activity, while women who are sexually inactive express satisfaction with their sexual function and have low interest in learning about treatments [4, 8]. Patients after transplantation may have lower sexual desire but have stable high relationship and life satisfaction.

This chapter examines the evidence for management of sexual dysfunction in adults with CKD.

Definition

Sexual dysfunction includes a range of clinical symptoms and experiences among people with CKD. A formal definition of sexual dysfunction is provided by DSM-5 [2]. Sexual dysfunction among men is categorized as erectile dysfunction, low sexual desire, delayed ejaculation, and altered sexual function related to substances or medication and other causes. Among women, abnormalities are altered sexual interest and arousal, genital and pelvic pain or pain on penetration, and altered sexual function due to substances or medications in addition to other causes. The DSM-5 indicates that for sexual dysfunction to be clinically present, it should occur at a frequency of 75–100% of the time for at least 6 months and lead to significant distress. Importantly, sexual dysfunction is excluded as a primary diagnosis when it might be explained by an alternative mental health diagnosis as a consequence of severe relationship distress (e.g. partner violence) or other significant stressors.

Epidemiology

The heterogeneity in clinical abnormalities of sexual dysfunction and the ability of diagnostic tools to measure the presence of clinical distress makes it difficult to determine its exact prevalence in patients with CKD. The prevalence of sexual dysfunction as measured by clinical scales, particularly for women, is highly dependent on sexual activity and the presence of a partner. The prevalence also depends on the stage and duration of CKD.

Hypogonadism (lower estrogen and testosterone release) occurs in 40–60% of patients treated with hemodialysis and 15–40% of people with CKD stages 1 to 4, and decreases in parallel with kidney function [9, 10]. The prevalence of erectile dysfunction is highly variable across existing studies (25–90%) and is probably more commonly experienced by men requiring dialysis that those with earlier stages of CKD and recipients of a kidney transplant [3]. It is unclear whether erectile dysfunction improves after kidney transplantation and is likely to relate to age, coexisting low testosterone levels, and comorbidity [11]. Available studies in CKD frequently use the International Index of Erectile Function (IIEF) to assess erectile function, although this measure evaluates symptoms limited to the previous 4 weeks and does not assess the psychological impact of erectile dysfunction on men [12].

The prevalence of sexual dysfunction in women with CKD has commonly been assessed using the 9-item Index of Female Sexual Function (IFSF) score and the 19-item Female Sexual Function Index (FSFI) score [13, 14]. These measures adjudicate that sexual dysfunction is present when a woman is sexually inactive, leading to widely disparate estimates of prevalence based on whether cohort analyses include or exclude sexually inactive women and those without sexual partners. In a recent large multinational cohort study of 1309 women treated with dialysis, about half responded to questionnaires and of the respondents nearly two-thirds reported no sexual activity, while the remaining one-third reported generally low sexual function across the domains measured (desire, arousal, lubrication, pain, satisfaction, and orgasm) [15]. In a different cohort of women treated with hemodialysis and participating in a clinical trial of symptom management strategies, sexual dysfunction was largely related to sexual inactivity in 82% of assessments [4]. Sexual inactivity was most frequently due to a lack of interest (43%) or partner (39%), while sexual difficulty was rare (2%). Approximately 5% of women expressed an interest in learning about the causes and treatment for sexual dysfunction in that study. Increasing focus on the need to measure distress related to sexual function as a component of the patient experience has resulted in the development and validation of scales to quantify sexual and relationship distress [16]. In 27 women with CKD and creatinine clearance ≤30 ml/min and not receiving dialysis, 44% reported distress compared with 22% of age-matched women without CKD [17].

Sexual dysfunction may persist after kidney transplantation despite resolution of abnormalities in the hypothalamic-pituitary-gonadal system. In a cross-sectional study, just over half of male kidney transplant recipients who were sexually active met criteria for erectile dysfunction [18].

Pathophysiology

Sexual dysfunction is multifactorial in CKD. Contributing causes include the hormonal changes associated with CKD leading to altered functioning of the hypothalamic-pituitary-gonadal axis, comorbidity including hypertension and vascular disease leading to altered blood flow to erectile tissues, medications, anxiety and depression, altered life priorities, and competing causes of distress that may lead to partner

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and relational challenges (Figure 77.1). Disturbances in the pituitary-gonadal axis occur with moderate kidney disease, are not recovered with renal replacement therapy, but may be reversed by kidney transplantation.

Progressive kidney disease and uremia alter the amino acid neurotransmitter outflow from the hypothalamus, leading to reduced pulsatile release of gonadotropin-releasing hormone (GnRH), and lower gonadotrophin synthesis and secretion [19]. Altered calcium and phosphorous levels in CKD also alter gonadotrophin release. Circulating plasma levels of LH are increased with renal impairment due to decreased clearance. Peak release of LH during pulsatile secretion is decreased, leading to lower serum testosterone levels, resulting in the diminished normal feedback suppression of LH by testosterone [20, 21]. Pulsatile release of LH may be completely absent for women with CKD.

Prolactin levels are commonly increased in men and women with CKD, and may result from autonomous secretion, normally inhibited by dopaminergic control. Hyperprolactinemia is linked to fertility, loss of libido, low testosterone concentrations, and inappropriately low LH in men with normal kidney function [22]. Zinc deficiency is common in CKD and may be associated with impaired gonadal function.

CKD may also directly impact ovarian and testicular hormones in addition to impairing function of the hypothalamus and pituitary tissues. Low testosterone levels occur for men due in part to reduced production, decreased free testosterone levels, and increased clearance, which result in decreased spermatogenesis. For women, uremia leads to loss of cyclical estradiol levels and impaired luteinization of follicles, impairing the normal rise in progesterone levels in the second half of the menstrual cycle [23, 24]. Altered cyclical hormones lead to anovulation, dysfunctional uterine bleeding, and infertility. In men, CKD is associated with impaired maturation of sperm and aplasia

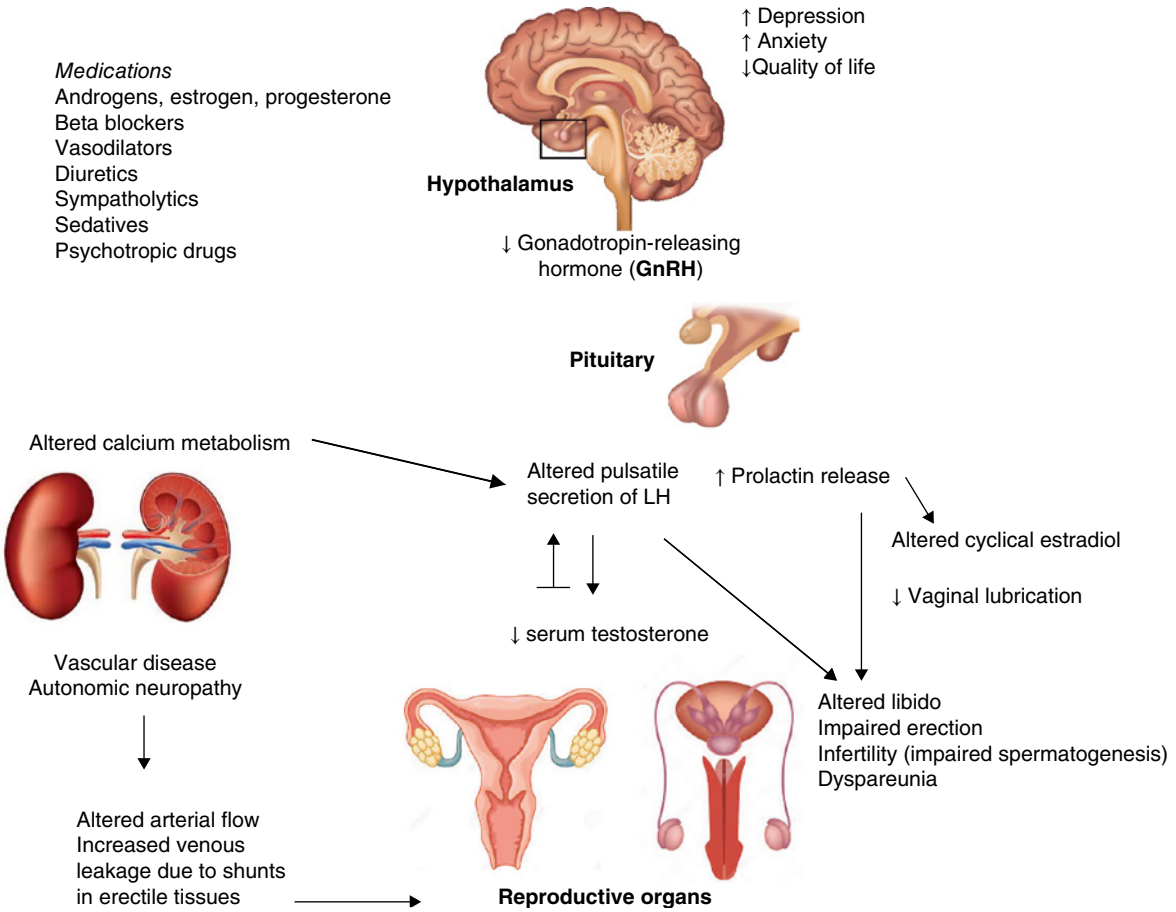

Figure 77.1 Pathogenesis of sexual dysfunction in chronic kidney disease. Some of the complex relationships between the hypothalamic, pituitary, and gonadal activity in adults with chronic kidney disease. Normal hypothalamic function is lost, leading to impaired gonadotrophin-releasing hormone (GnRH) and loss/decrease in pulsatile luteinizing hormone (LH) release. Increased prolactin levels impact the axis and hormonal release by ovarian and testicular tissues. Accelerated vascular disease and neuropathy impact erectile function directly, while circulating levels of testosterone and cyclical estradiol levels are reduced. Medications and cognitive stressors, depression, and anxiety all act to increase social and relational distress that may increase sexual dysfunction.

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of germinal elements, damage to seminiferous tubules, interstitial fibrosis, and calcification.

Normal erectile function for men requires adequate arterial penile flow and smooth muscle action to block blood efflux from the cavernous space. Accelerated vascular disease may impair intracavernosal arterial blood pressure, even without clinical evidence of peripheral vascular disease. Men with CKD may first experience delayed erection, then subsequently reduced penile rigidity and nocturnal penile tumescence, and complete erectile loss. Penile erection is a complex sequence of changes in arterial vascular smooth muscle tone that may be impaired by neuropathy associated with renal failure. Medications, including antihypertensive therapies, may directly impair erectile function in CKD.

While the prevalence of depression and anxiety may be increased for men and women with CKD, there is conflicting evidence about the relationship between these conditions and sexual dysfunction among those with CKD [3, 25]. In a systematic analysis of cohort and cross-sectional studies, depression was frequently identified as a variable that showed significant association with sexual dysfunction in several studies [3].

Kidney transplantation is associated with reversal of the hormonal and endocrine abnormalities linked to sexual dysfunction among patients with end-stage kidney disease and may be associated with lower frequency of perceived sexual dysfunction [26–28].

Diagnosis

Men

Clinical History and Examination

The clinical diagnosis of sexual dysfunction is based on a thorough history and clinical examination to identify the primary issue (e.g. erectile dysfunction, low libido, infertility). Table 77.1 lists the potential factors involved in the pathogenesis of sexual dysfunction for men with CKD that can guide clinical inquiry and examination, and investigation.

During the clinical history-taking, a sexual, psychosocial, and medication history should be explored. A brief sexual symptom checklist may assist to identify the priority symptoms experienced by male patients (Table 77.2) [30]. There is no robust evidence from randomized controlled trials (RCTs) that screening for sexual dysfunction among patients with CKD improves patient-centered outcomes; systematic screening for sexual dysfunction in CKD is not currently recommended based on a lack of available evidence.

Table 77.1 Factors involved in sexual dysfunction in men with chronic kidney disease.

Gonadal function
Decreased testosterone production
Impaired spermatogenesis
Hypothalamic–pituitary function
Blunted increase in luteinizing hormone (LH) levels
Decreased amplitude of pulse LH release
Variable increase in FSH levels
Increased prolactin levels
Vascular disease
Impaired arterial inflow and venous drainage of penis
Autonomic neuropathy
Psychological factors
Anxiety
Depression
Medications
Sympatholytic
Beta blocker
Vasodilator
Diuretic
Sedative
Psychotropic drug
Altered calcium metabolism leading to altered pituitary function

Source: Adapted from Palmer [29].

Table 77.2 Brief sexual symptom checklist: men.

Over the previous 3 mo or more:

1) Are you satisfied with your sexual function?
2) If no, how long have you been dissatisfied with your sexual function?
3) The problem with your sexual function is: (all that apply)
   1) Problems with little or no interest in sex?
   2) Problems with erection?
   3) Problems with ejaculating too early during sexual activity?
   4) Problems taking too long, or not being able to ejaculate or have orgasm?
   5) Problems with pain during sex?
   6) Problems with penile function during erection
   7) Other
4) Which problem is most bothersome?
5) Would you like to discuss this problem?

Source: Based on Hatzichristou et al. [30].

Self-rating scales are available to evaluate for the presence of sexual dysfunction. Most published studies have used the full (15-item) or shorter (5-item) versions of the IIEF [12]. The IIEF is considered a screening instrument

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for the presence and severity of erectile dysfunction in the 5-item scale, and additionally orgasmic function and sexual interest in the full questionnaire. Cut-off scores in the IIEF scale for men have been proposed based on diagnostic accuracy analyses against blinded clinician interviews in the general population, although the diagnostic utility of these scales have not been critically appraised in the setting of CKD.

Based on the potential factors causing sexual dysfunction in CKD, a targeted history and examination exploring for presence of vascular disease, autonomic neuropathy, hyperparathyroidism, anxiety, depression, and medications is appropriate. Signs of peripheral vascular disease may indicate a contribution of arterial vascular disease to erectile dysfunction, although normal peripheral vascular findings do not exclude penile arterial abnormalities. Loss of secondary sexual characteristics (pubic, facial, and axillae hair, decreased muscle, and bone mass) suggest hypogonadal function. Features of autonomic neuropathy such as postural hypotension, loss of sweating, nocturnal diarrhea, urine retention, or loss of sinus arrhythmia may indicate a neuropathic contribution to sexual dysfunction. As men may have more than one factor contributing to sexual dysfunction, the finding of a physical abnormality can guide investigation and treatment, however additional causes still need to be considered and evaluated.

Investigations

Based on the likely etiology, investigations to evaluate for vascular disease and autonomic neuropathy may provide information about the possible factors leading to sexual dysfunction in men. These include Doppler ultrasound of the peripheral vasculature, remaining cognizant of the fact that erectile dysfunction may occur before the onset of clinically-apparent vascular disease [31]. Penile duplex Doppler ultrasound is rarely used as a diagnostic tool, and a systematic analysis in studies of men without CKD suggests there is currently a lack of standardization in performance and interpretation, and diagnostic cut-off values are extremely heterogeneous [32]. Assessment of autonomic neural function at the bedside may include testing for orthostatic hypotension without compensatory increased heart rate. Specific features of neurogenic bladder function may suggest a neuropathic origin to erectile dysfunction.

Endocrine testing that may assist to identify specific hormonal factors includes measurement of serum LH, FSH, testosterone, and prolactin levels. While patients with CKD have elevated prolactin levels, a serum prolactin level greater than 94 μg/l is discriminatory for a prolactinoma [33] and levels above 500 μg/l are diagnostic of a macroprolactinoma [34]. In the presence of serum prolactin levels >100 μg/l, imaging of the hypothalamic-pituitary region would be appropriate. Total serum testosterone should be measured early in the morning on at least two occasions in the absence of acute illness. A total testosterone level <10 nmol/l (300 ng/deciliter) suggests low testosterone, although the serum results should be interpreted in conjunction with symptoms [35]. Serum zinc levels may indicate zinc deficiency as a factor contributing to gonadal failure. Screening for depression or anxiety may be appropriate.

Women

Clinical History and Examination

As for men, the clinical diagnosis of sexual dysfunction is based on a thorough history and clinical examination to identify the key clinical issues, including menstrual disorders, infertility, and/or symptoms including vaginal dryness, pain or discomfort during sexual intercourse, low libido, decreased genital sensation, or difficulties with orgasm. Table 77.3 lists the potential factors contributing to sexual dysfunction for women.

Table 77.3 Factors involved in sexual dysfunction in women with chronic kidney disease.

Gonadal function
Anovulatory cycles
Loss of progesterone release
Hypothalamic-pituitary function
Blunted increase in luteinizing hormone levels
Decreased amplitude of pulse luteinizing hormone release
Low estradiol levels
Variable increase in follicle-stimulating hormone levels
Increased prolactin levels
Vaginal pathology
Vaginal dryness
Vaginal atrophy
Vascular disease
Impaired arterial inflow in genital tissue
Autonomic neuropathy
Psychological factors
Anxiety
Depression
Medications
Sympatholytic
Beta blocker
Vasodilator
Diuretic
Sedative
Psychotropic drug
Altered calcium metabolism leading to altered pituitary function

Source: Adapted from Palmer [29].

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During the clinical history-taking, a sexual, psychosocial, and medication history should be explored. Specific questioning should include a menstruation history, including assessments for the presence of irregular menses, menorrhagia, and amenorrhea, and local vaginal symptoms including dryness and pain or discomfort on penetration. A brief symptom checklist may assist in the assessment of sexual dysfunction for women, including an understanding about whether women wish to discuss the problem (Table 77.4). Specific inquiry about the age of onset, frequency, distress, and partner-related issues are relevant. As for men, there is no high-certainty evidence that routine screening for sexual dysfunction in women with CKD improves clinical outcomes.

In women with CKD, the 19-item FSFI [14] is commonly used to evaluate six domains of sexual dysfunction (desire, arousal, lubrication, orgasm, global satisfaction, and pain) in the 4 weeks before questionnaire completion. Sexual inactivity leads to lower scores for rating items and may classify individuals who are sexually inactive as having sexual dysfunction. The diagnostic utility of the FSFI to identify sexual dysfunction causing distress for women with CKD is unknown. A modified FSFI can identify the reasons for sexual inactivity and whether the woman is interested in hearing more about the causes and treatments for sexual dysfunction [4].

Identification of sexual dysfunction causing distress should prompt a targeted history and examination to evaluate for presence of vascular disease, autonomic neuropathy, local genital, vaginal, and uterine abnormalities, secondary sexual characteristics, and hyperparathyroidism.

Investigations

Targeted investigation may identify a specific factor contributing to sexual dysfunction. Laboratory testing should be guided by patient symptoms and examination findings.

Table 77.4 Brief sexual symptom checklist: women [30].

Over the previous 3 months or more:

1) Are you satisfied with your sexual function?
2) If no, how long have you been dissatisfied with your sexual function?
3) The problem with your sexual function is: (all that apply)
   1) Problems with little or no interest in sex?
   2) Problems with decreased genital sensation?
   3) Problems with decreased vaginal lubrication (dryness)?
   4) Problems reaching orgasm?
   5) Problems with pain during sex?
   6) Other
4) Which problem is most bothersome?
5) Would you like to discuss this problem?

Source: Based on Hatzichristou et al. [30].

The presence of menstrual abnormalities may prompt physical examination and uterine ultrasound to investigate for uterine fibroids and other abnormalities. Vaginal symptoms will prompt specific evaluation of vaginal tissue. Endocrine testing may assist to identify women with low serum estradiol levels and elevated circulating prolactin concentrations that warrant imaging (pituitary-hypothalamic) and targeted treatment (estrogen or bromocriptine). Screening for depression or anxiety may be appropriate.

Treatment

The wide range of factors that result in sexual dysfunction with CKD has led to attempts to improve symptoms through targeting of specific pathophysiological factors. Knowledge of the cause of sexual dysfunction for an individual patient may help identify an appropriate therapeutic strategy. Regardless of the cause and putative treatment, the evidence base for treatment of sexual dysfunction in the setting of CKD is of low certainty, limiting the availability of evidence-based recommendations (Tables 77.5 and 77.6) [7]. In a Cochrane review of interventions for sexual dysfunction, 15 studies involving 352 participants were identified, including 13 in dialysis patients and two involving recipients of a kidney transplant [7]. All but one study included only men.

Phosphodiesterase-5 Inhibitors

Phosphodiesterase-5 (PDE) is an enzyme found in the smooth muscle of the corpus cavernosum that degrades cyclic guanosine monophosphate (GMP). PDE inhibitors (sildenafil, vardenafil, tadalafil, and avanafil) competitively bind to PDE_5 and inhibit the hydrolysis of cyclic GMP to increase the action of nitric oxide. This results in smooth-muscle relaxation in the corpus cavernosum and increased blood flow to the penis during sexual arousal.

Despite their widespread use, evidence for the effects of PDE inhibitors in men with CKD is limited to a few studies involving small numbers of men (Figure 77.2). Trials have evaluated vardenafil in 60 male transplant recipients [41] and 39 dialysis patients [42], and sildenafil in 68 dialysis patients [43, 44] and 32 transplant recipients [45]. Evidence from placebo-controlled trials is of very low certainty due to methodological limitations in studies, heterogeneity in the results between studies, and limited evidence for each of the stages of CKD. Based on a minimally important clinical difference in score for a single IIEF domain estimated of 2 for men with mild dysfunction, 5 for men with moderate

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Table 77.5 Treatment for sexual dysfunction in men with chronic kidney disease.

Treatment	Recommendation	Certainty of evidence	Strength of recommendation
Phosphodiesterase-5 inhibitors	We suggest that men treated with dialysis may reasonably choose to use or not to use phosphodiesterase-5 inhibitors based on the very low certainty that treatment makes a difference to erectile function scores, erection frequency, erection quality, penetration ability, frequency of penetration, and maintenance of erection after penetration. We suggest that the certainty of the evidence for phosphodiesterase-5 inhibitors to manage sexual dysfunction for men with earlier stages of chronic kidney disease or with a kidney transplant is so low that a recommendation regarding use in clinical practice is too speculative.	*Very low* (overall satisfaction, intercourse satisfaction, libido, erectile frequency, erectile quality, penetration ability, maintenance frequency of penetration, maintenance of erection after penetration, erection confidence) *Very low or absent* (adverse events including headache; coronary ischemia).	Weak: men with chronic kidney disease stage 5D [7] No recommendation: men with chronic kidney disease stage 1–5 and 5T
Testosterone replacement	We suggest that the certainty of the evidence for testosterone replacement to manage sexual dysfunction is so low that a recommendation regarding use in clinical practice is too speculative	*Very low* (data from randomized controlled trials are absent; data from observational studies suggest variable efficacy and adverse event)	No recommendation [36, 37]
Bromocriptine	We suggest that the certainty of the evidence for bromocriptine to manage sexual dysfunction is so low that a recommendation regarding use in clinical practice is too speculative	*Very low or absent* (outcome data limited to testosterone levels)	No recommendation [7]
Zinc supplementation	We suggest that the certainty of the evidence for zinc supplementation to manage sexual dysfunction is so low that a recommendation regarding use in clinical practice is too speculative	*Very low or absent* (intercourse frequency, libido)	No recommendation [7]
Vitamin E	We suggest that the certainty of the evidence for vitamin E supplementation to manage sexual dysfunction is so low that a recommendation regarding use in clinical practice is too speculative	*Very low or absent* (outcome data limited to hormone levels; adverse event data absent)	No recommendation [7]
Vacuum detumescence device	We suggest that the certainty of the evidence for vacuum tumescence therapy is so low that a recommendation regarding use in clinical practice is too speculative	*Very low* (data from randomized controlled trials are absent; data limited to 26 men treated with dialysis in observational study)	No recommendation [36]
Penile prostheses, intracavernous injections, transurethral injections	We suggest that the certainty of the evidence for local surgical interventions is so low that a recommendation regarding use in clinical practice is too speculative	*Very low* (data from randomized controlled trials are absent; data limited to small numbers of men in observational studies)	No recommendation [38]
Psychotherapeutic/ psychoeducational interventions	We suggest that the certainty of the evidence for psychotherapeutic/ psychoeducational interventions is so low that a recommendation regarding use in clinical practice is too speculative	*Very low* (data from randomized controlled trials are absent)	No recommendation [7]

These recommendations reflect a belief that most men would place high value on effectiveness of treatment and would wish to avoid risks of adverse events, and place low value on minimizing drug and treatment expenditure. GRADE assessment of the certainty of the evidence[39]: High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different* is low. Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different* is moderate. Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different* is high. Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different* is very high. **Substantially different = a large enough difference that it might affect decision-making*.

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Table 77.6 Treatment for sexual dysfunction in women with chronic kidney disease.

Treatment	Recommendation	Certainty of evidence	Strength of recommendation
Phosphodiesterase-5 inhibitors	We suggest that the certainty of the evidence for phosphodiesterase-5 inhibitors to manage sexual dysfunction is so low that a recommendation regarding use in clinical practice is too speculative	*Very low or absent* (data from randomized controlled trials are absent)	No recommendation [7]
Testosterone	We suggest that the certainty of the evidence for testosterone to manage sexual dysfunction is so low that a recommendation regarding use in clinical practice is too speculative	*Very low or absent* (data from randomized controlled trials are absent)	No recommendation [7]
Bromocriptine	We suggest that the certainty of the evidence for bromocriptine to manage sexual dysfunction is so low that a recommendation regarding use in clinical practice is too speculative	*Very low or absent* (outcome data limited to testosterone levels)	No recommendation [7]
Estrogen	We suggest that the certainty of the evidence for estrogen to manage sexual dysfunction is so low that a recommendation regarding use in clinical practice is too speculative	*Very low or absent* (data from randomized controlled trials are absent)	No recommendation [7]
Pelvic floor exercises	We suggest that the certainty of the evidence for pelvic floor exercises to manage sexual dysfunction is so low that a recommendation regarding use in clinical practice is too speculative	*Very low or absent* (data from randomized controlled trials are absent)	No recommendation [7]
Psychotherapeutic/psycho-educational	We suggest that the certainty of the evidence for psychotherapeutic/psycho-educational interventions is so low that a recommendation regarding use in clinical practice is too speculative	*Very low or absent* (data from randomized controlled trials are absent)	No recommendation [7]

These recommendations reflect a belief that most women would place a high value on avoiding risks of adverse events and uncertain treatments. GRADE assessment of the certainty of the evidence [39]: High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different* is low. Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different* is moderate. Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different* is high. Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different* is very high. **Substantially different = a large enough difference that it might affect decision-making*.

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dysfunction, and 7 for men with severe dysfunction [40], it is uncertain whether PDE_5 inhibitors provide clinically important improvements in erectile function (Table 77.5). Evidence related to adverse events with PDE inhibitor therapy was of very low certainty. Based on a belief that most men would place high value on effectiveness of treatment and would wish to avoid risks of adverse events, placing low value on minimizing drug and treatment expenditure, it would be reasonable to trial treatment with a PDE inhibitor in men who wish to do so, being cautious not to coprescribe with nitrate therapy or in men with coronary artery disease. Data for women are insufficient to inform clinical decision-making [7].

Testosterone

Sexual dysfunction in men with CKD may be associated with low testosterone levels. However, there are no RCTs investigating long-term outcomes of testosterone replacement therapy in men with end-stage kidney disease. Observational studies are available. In six men with end-stage kidney disease, intramuscular testosterone enanthate 400 mg once weekly increased serum testosterone [46]. Oral testosterone undecanoate 240 mg daily in 19 dialyzed men restored pituitary responsiveness to LH and lowered serum prolactin [47]. Testosterone given as a depot injection to 27 men with biochemical hypogonadism and treated with vacuum tumescence therapy with continued erectile dysfunction provided full restoration of a sexual response in three men, of whom two gradually lost the response over 18 months [36]. These data suggest while testosterone replacement may increase serum testosterone levels and improve pituitary function, treatment does not provide long-term improvement in sexual dysfunction. Testosterone replacement has insufficient evidence among women with CKD.

Bromocriptine

Bromocriptine is a dopamine agonist that is used in the treatment of high prolactin levels and associated conditions including hypogonadism, amenorrhea, and infertility. Bromocriptine is a potential treatment for hypogonadism.

In a previous systematic review of randomized trials, bromocriptine (5–7.5 mg/day) for 3–8 months was administered in two crossover studies involving 40 men treated with hemodialysis [48]. In a crossover trial in 15 men, seven completed an 8-week treatment period, with serious hypotension precluding bromocriptine therapy in the remaining eight men, with other side effects including nausea, vomiting, diplopia, and loss of appetite. Bromocriptine reduced prolactin levels, and increased intercourse frequency and erection quality [48]. Similarly, in 25 men on hemodialysis with erectile dysfunction, bromocriptine led to withdrawal due to side effects in one-third of men, while perceived sexual function was improved when men received bromocriptine [49]. Based on methodological limitations and heterogeneity in treatment outcomes, the evidence certainty for these findings is very low and insufficient to guide clinical decision-making about bromocriptine for men with sexual dysfunction. Treatment with bromocriptine in three women with end-stage kidney disease and hyperprolactinemia did not have a consistent effect on gonadotropin responses [23].

Clomiphene

Clomiphene is sometimes used for men with hypogonadism and may increase serum testosterone levels [50]. In an uncontrolled study in five men with CKD and androgen deficiency, clomiphene citrate at 100 mg/day increased serum testosterone, LH, and FSH, although the effect on spermatogenesis and other patient outcomes was inconclusive or not measured [51].

Estrogen

CKD causing low circulating estradiol concentrations can lead to vaginal dryness and atrophy, causing pain or discomfort during intercourse. Women may benefit from local estrogen therapy or lubricant, although data specific to women with CKD is limited. There are no randomized trials evaluating the benefits or harms of estrogen therapy on sexual function for women with kidney disease.

Zinc Replacement

Zinc deficiency may be a factor in gonadal dysfunction and is present in men with CKD. Zinc replacement in oral form (elementary zinc or zinc acetate) [52] or in dialysate (400 μg/l) [53–55] has been evaluated in four RCTs involving 50 men treated with hemodialysis. Treatment was administered for a range of 1.5–6 months. Evidence for the effects of zinc therapy on sexual dysfunction was limited to one or two trials for each evaluated outcome (serum testosterone, plasma FSH and LH, intercourse frequency, erectile dysfunction, libido, nocturnal penile tumescence), leading to very low certainty in the results. The effects of zinc supplementation for sexual dysfunction in men with CKD are speculative and trials are not sufficiently robust to assist clinical decision-making. If men place high value on a trial of therapy and lower value on treatment certainty, evidence from a single trial suggests oral zinc replacement may improve erectile dysfunction [52]. Data for zinc replacement on sexual function in women with CKD are absent.

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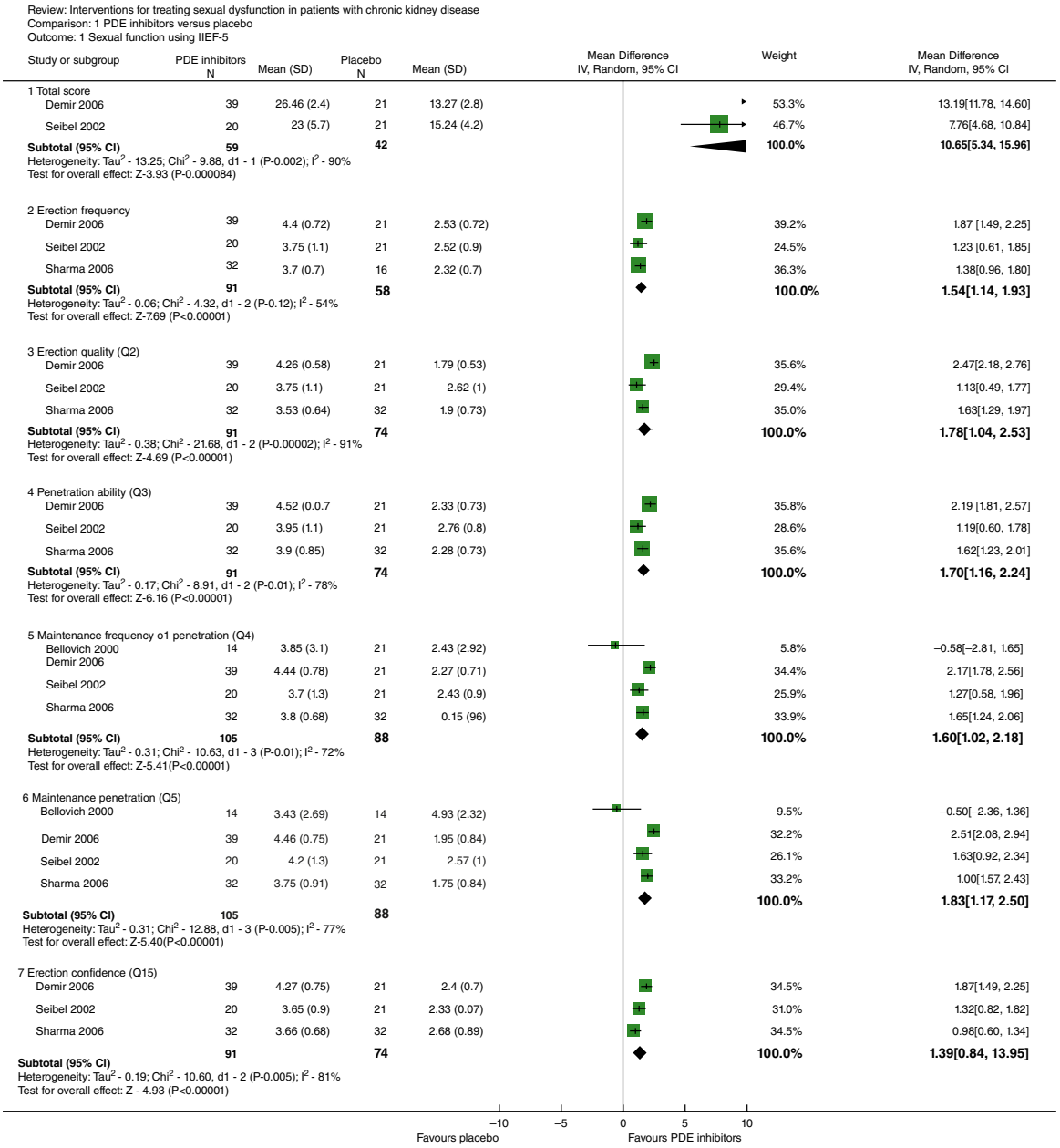

Figure 77.2 Effect of phosphodiesterase-5 inhibitors on sexual function in men with chronic kidney disease. Analysis obtained from Vecchio et al. [7]. Weight refers to the contribution of each study to the overall estimate of treatment effect. The pooled estimate is calculated by using a random effects model. Proportion of studies including dialysis/CKD/transplant. Treatment estimates are expressed as a mean difference with a 95% confidence interval. The minimal clinically important difference in the erectile function domain (question 7) of the International Index of Erectile Function scale (IIEF) is 2 for men with mild dysfunction, 5 with moderate dysfunction, and 7 with severe dysfunction. *Source:* Rosen et al. [40].

Vitamin E

Vitamin E is prescribed for sexual dysfunction based on the potential role of oxidative stress in erectile dysfunction [56]. In a single trial involving 24 men on hemodialysis, oral vitamin E (300 mg/day) was compared with placebo for 8 weeks with a focus on endocrine outcomes, including serum LH, FSH, free testosterone, and prolactin concentrations [57]. Prolactin levels were reduced by vitamin E therapy, while serum LH, FSH, and free testosterone were not altered. It is uncertain whether vitamin E has any effect on patient-centered sexual function outcomes.

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Vitamin D

Altered calcium metabolism secondary to CKD may alter the pulsatile secretion of LH (Figure 77.1). In a single trial among men treated with hemodialysis, low serum testosterone, and elevated serum parathyroid hormone levels, calcitriol therapy for 2–4 months had no evidence of effect on libido, intercourse frequency, or masturbation, despite lowering serum parathyroid hormone concentrations [58]. No randomized trials are available for evaluating vitamin D therapy on sexual function in women with CKD.

Vacuum Tumescence Device

A vacuum device consisting of a plastic cylinder that is placed over the penile shaft with a pump used to generate negative pressure to draw blood into erectile tissue has not been evaluated in randomized trials in men with CKD. In a nonrandomized study, the outcomes of a vacuum tumescence device in 26 men treated with dialysis and who had biochemically proven hypogonadism have been reported. Men used the devices after partial response to testosterone replacement [36]. Of these men, 19 experienced full correction of erectile dysfunction, while five did not experience benefit. Based on these data, men who place a high value on treatment of their condition and lower value on evidence uncertainty may reasonably wish to consider vacuum tumescence therapy, although the existing evidence is of very low certainty. Data are limited to the dialysis setting.

Penile Prostheses, Intracavernous Injections, and Transurethral Injections

Evidence for surgical interventions to treat erectile dysfunction are limited to observational data and case series, and evidence is of very low certainty. Information is more commonly provided among recipients of a kidney transplant. In seven men, four penile prostheses implanted after transplantation were effective and no complications were reported up to 40 months following implantation, while of five prosthesis implanted before transplantation, two were removed due to infection, one was removed due to leakage, and one led to sepsis [59]. In another case series in 12 men treated with dialysis or transplantation, 11 men maintained a prosthesis over 8 years, while three required reimplantation due to mechanical failure and one was explanted due to infection [38]. Data are absent for intracavernosal and transurethral injections among men with kidney disease.

Psychotherapeutic and Psychoeducational Interventions

Evidence to support psychological and psychosocial interventions such as group psychotherapy and focused sex group therapy on sexual function and erectile dysfunction is limited. No RCTs have been identified for evaluating these interventions of sexual function in men or women with CKD.

Patient and Partner Needs and Preferences

Reporting of patient experiences, needs, and preferences related to sexual function in the context of CKD is limited. This information is needed to offer insights into the level of distress and patient perspectives on treatment preferences that can shape the future research priorities on sexual dysfunction.

In a structured interview study among 68 men and women treated with peritoneal dialysis for 3 months or longer, 63% of patients reported never having intercourse, 19% had intercourse two times per month or less, and 18% had intercourse more than two times per month [8]. Among those not having intercourse, 44% of patients (mostly men) expressed a desire to have intercourse. Patients reporting a higher frequency of intercourse had lower scores on assessments of depression, anxiety, and physical symptoms.

In women receiving long-term hemodialysis and as part of a clinical trial of symptom management, those who were not sexually active were asked about their reasons for not being sexually active and their preferences about treatment for sexual dysfunction [4]. In 815 assessments women reported they were not sexually active due to lack of interest (43%) and lack of partner (39%). Of those women who reported a lack of interest, 76% were moderately to very satisfied with their sex life. In 5% of assessments, women reported an interest in learning about the causes or treatment of sexual dysfunction. Overall, these findings suggest women on dialysis maintain high levels of satisfaction despite sexual inactivity and have low interest in considering treatment.

After kidney transplantation, patients reported wishing less sexual activity and lower sexual drive, although rates of masturbation and orgasm were unchanged [6]. Despite these changes, 90% of patients reported high relationship and life satisfaction. Similarly, the wish for sexual activity and frequency of sexual activity among partners decreased, and the high personal importance of sexual satisfaction decreased. Couples did not consider separating and partners also reported maintaining high relationship and life satisfaction.

Conclusions

In conclusion, sexual dysfunction may be frequent among men and women with CKD and is caused by a range of endocrine, biochemical, and psychological factors.

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Patients may frequently be sexually inactive, although the impact of this on patient lives is incompletely known and may be less than previously thought. Lower sexual activity and desire are uncoupled from life and partner satisfaction among dialysis and transplant patients and partners. There is limited evidence to support clinical decision-making for treatments in this condition. Few women are interested in treatment. Men and women who value treatment efficacy and place lower value on certainty of treatment outcomes may wish to trial treatment based on the cause of their sexual dysfunction. Evidence supporting estrogen or testosterone therapy and PDE inhibitors is of very low certainty due to a lack of robust clinical trials.

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Family and Caregiver Support

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Introduction

The aging population and increasing prevalence of chronic kidney disease (CKD) globally has resulted in an increased burden being placed on informal caregivers, namely family members or friends, to provide support and care [1]. Informal caregivers of patients with CKD take on a broad span of responsibilities in care coordination, ranging from management of CKD and related conditions (administering medications, applying dressings, symptom control, health monitoring), to planning and organization (transportation, appointments, supporting dietary and nutritional intake), and personal and emotional care (personal hygiene, decision-making, companionship, and psychological support) [2, 3]. In addition, caregivers of patients using home-based kidney replacement therapies, such as peritoneal dialysis (PD) or home hemodialysis (HD), may need to assist patients in using complex medical equipment such as dialysis machines, catheters, and needles.

These ongoing responsibilities contribute to caregiver burden and can lead to depression, stress, fatigue, isolation, and an inability to cope in caregivers [4–7]. Support interventions, including training, education, and psychosocial care may assist caregivers and improve their quality of life and patient outcomes [1]. This chapter examines the evidence on caregiver burden and support interventions for caregivers of people with CKD.

Caregiver Burden

Caregiver burden is defined as the physical, financial, and psychosocial hardships of caring for someone with a disease or medical condition [8]. This occurs when the demands of care exceed the resources available to cope with these demands [9, 10]. Studies have shown that the majority of caregivers of patients with CKD report moderate to severe burden [11–14].

Factors Contributing to Caregiver Burden

Caregiver burden is associated with declines in the functional and cognitive status of the patient [15–19]. These challenges are highly relevant among caregivers of patients with CKD, as CKD is associated with a multitude of comorbidities which affect a patients' physical function and cognitive capacity [20, 21]. Caregiver burden is associated with the numbers of years the patient has been on dialysis ($r = 0.82$, $P < 0.001$) and the number of hours of care provided per day ($r = 0.30$, $P < 0.001$) [11].

Depression is both a risk factor for and an outcome of caregiver burden [22, 23], with higher levels of depression and anxiety relating to higher levels of burden [13]. This is shown across other chronic diseases, including cardiovascular disease, dementia, and cancer [9, 24, 25].

In low- and middle-income countries, the shortage of resources, infrastructure, and healthcare personnel can place increased burden on caregivers [26]. Family caregivers provide care to their patients even while hospitalized due to the shortage of nursing staff [27]. Additionally, tertiary care centers are usually located in urban areas, meaning that there is a requirement for families living in rural areas to relocate for the patient to access medical care, causing social and financial disruptions [28, 29].

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Burden of Caregiving Across Stages of Treatment

The nature, severity, and intensity of the burden experienced by caregivers of patients with CKD may vary depending on the type of kidney replacement therapy. For patients on home HD, some caregivers are integrally involved in the treatment, and this can be physically and cognitively demanding [30, 31]. Caregivers of patients on home HD have a higher perceived caregiver burden compared to conventional in-center HD [32]. For patients receiving in-center HD, caregivers may have additional tasks such as organizing or providing transport for patients. Some caregivers of patients on PD may be involved in technical aspects of dialysis, managing and preventing complications (e.g. infection), and physical aspects such as storing, moving, and disposing of large volumes of dialysis fluids [33]. Elderly patients on continuous ambulatory peritoneal dialysis (CAPD) have an increased risk of transfer to HD if they are experiencing psychosocial difficulty, including caregiver problems [34]. Caregivers of patients with end-stage kidney disease and not receiving kidney replacement therapy may have to contend with the emotional toll and distress as the patient's health deteriorates.

Caregivers of Children with CKD

Caregivers of children with CKD experience considerable psychological, social, and financial stress [35]. Caregivers, usually parents, are required to be "on-call" at all times and take on the role of healthcare provider. They are required to perform invasive and painful procedures (e.g. nasogastric intubation, needles, cannulation) that cause pain and discomfort for the child, which may conflict with their parental role of protecting their child, causing stress [29]. Additionally, parents who perceive themselves as lacking in technical expertise or ability and unable to perform these duties can feel disempowered in having to relinquish caregiving roles to health professionals, which can result in feelings of guilt or inadequacy [36]. Caregivers must help their child with CKD cope with unique challenges related to growth and development [5, 37]. In addition to managing the requirements of the child, parents must also bear the emotional toll of having a chronically ill child.

Parents of children on dialysis have a higher risk of depression compared to parents of healthy children (28% vs. 5%) and the general adult population (28% vs. 9%, $P = 0.001$) [5]. The mean scores in all four domains (physical, psychological, social relationships, and environmental quality) based on the World Health Organization Quality of Life (WHOQOL) measure were significantly lower for caregivers of children on dialysis compared to caregivers of healthy children. Parents associate their own health with that of the child, such that the health status of the caregiver is worse with increasing severity of their child's condition [38, 39].

Parents also face financial burden given the expenses incurred for treatment, medications, diet, accommodation, and transportation to clinics or the hospital, and may also have to take time off work [40–42]. Caregivers of children on dialysis were less likely to work full-time and earned less than caregivers of healthy children [5]. Low socioeconomic status is also associated with parental depression and anxiety, which can impact on the care and health of the child [41].

Measuring Caregiver Burden

A number of measures are available to assess caregiver burden. A systematic review on the burden of care and quality of life among caregivers for adults receiving dialysis identified a number of measures used [43], most frequently the Zarit Burden Interview (ZBI) [44]. The ZBI was originally developed to measure subjective burden among caregivers of adults with dementia. The 22-item self-report inventory examines burden associated with functional/behavioral impairments and the home care situation. Other measures frequently used include the Beck Depression Inventory [45], the Centre for Epidemiologic Studies Depression Scale [46], and the Medical Outcomes Study 36-Item Short Form Survey (SF-36, [47]).

Interventions

Interventions to support caregivers have the potential to improve outcomes for both the caregiver and the patient. Studies in cancer, dementia, stroke, and asthma have shown that education, information, psychosocial, and practical support interventions can improve caregiver burden, satisfaction, and quality of life [48–52], but there is limited evidence in CKD. A summary of findings is shown in Table 78.1.

A systematic review of support interventions for caregivers of people with CKD published in 2008 identified three studies, and all assessed the effect of educational materials on caregiver knowledge [1]. Two of the studies used a pre- and post-test study design to evaluate the impact of information provided to caregivers of dialysis patients [53, 54]. In the third study, participatory action research methods were used to develop an information handbook for transplant recipients and their caregivers [55]. All three studies found that the provision of

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Table 78.1 Summary of findings: interventions for caregivers.

Study ID	n	Setting	Participants	Study design	Summary of main findings
Tong et al. [40]	260	International	Caregivers of hemodialysis, peritoneal dialysis, and pediatric transplant patients	Systematic review	There is a need for the development and evaluation of interventions and services that address the informational and support needs of caregivers
Ismail et al. 2014	246	Netherlands	Family members of patients referred for transplant preparation or listed for deceased donor kidney transplantation	RCT	Improved knowledge scores, increase of self-efficacy of family members, improved attitude toward communication, greater willingness to donate
Fathima et al. [53]	30	India	Caregivers of adult HD patients	Pre- and post-test	Overall knowledge score improved
Tornay et al. [55]	135	Spain	Caregivers pediatric Tx patients	Participatory action research	Clarified doubts, diminished stress and fear, facilitated adaptation
Ghane et al. [56]		76	Family caregivers of hemodialysis patients	RCT	Improvements in quality-of-life scores
Chan et al. [58]		29	Caregivers of patients with CKD choosing not to be treated with dialysis or transplantation	RCT	Reduction in caregiver burden scores

CKD, chronic kidney disease; HD, hemodialysis; RCT, randomized controlled trial; Tx, transplantation.

information increased caregiver knowledge. However, the authors concluded that no high-quality evidence was available and that there is a need for the development and evaluation of interventions and services that address the informational and support needs of caregivers. No subsequent systematic reviews of interventions for caregivers of people with CKD have been conducted.

The following section reviews evidence for educational and psychosocial interventions for caregivers of patients with CKD.

Education and Psychosocial Support Interventions

Ghane et al. [56] conducted a randomized controlled trial (RCT) in Iran with 76 family caregivers of HD patients to examine the effect of home care training and problem-focused coping strategies on the quality of life of the caregivers. The intervention consisted of two training sessions focused on how to care for a patient on HD at home, and four training sessions on problem-focused coping strategies delivered by a psychiatric nurse which included communication skills, anger management, stress reduction, and deep breathing. An educational booklet was also provided to participants in the intervention group at the end of the first session. Participants in the control group only received routine training, which included pamphlets, and were provided with an educational booklet after the last assessment. The main outcome of the study was quality of life as measured by the 36-Item Short Form Health Survey (SF-36), which uses a scale ranging from 0 to 100, with higher scores reflecting a better quality of life. The survey was translated into Farsi and validated with this population [57]. The study found that participants in the intervention group had significant improvements in their quality-of-life scores from baseline to the end of the study (from 45.95 ± 14.94 to 63.51 ± 11.55; $t = 6.855$, df = 36, $P < 0.001$). The intervention group also had a significantly higher quality-of-life score compared to the control group at the end of the study (63.51 ± 11.55 vs. 41.74 ± 10.51; $t = 8.596$, df = 74, $P < 0.001$).

Chan et al. [58] conducted an RCT in Hong Kong with 29 pairs of patients with CKD choosing not to be treated with dialysis or transplantation and their caregivers. Caregivers in the intervention group received enhanced psychosocial support, which included education and psychosocial-spiritual support from an on-site palliative care nurse and social worker in a 30-minute session held once or twice monthly for up to 6 months. The first session assessed the needs of the caregivers through questions regarding the types of problems encountered with the patient, the type of information they would like to know, and how to better manage the patient's medical treatment. After the needs assessment, appropriate counseling and information were provided. The control group received standard renal care and caregivers were referred to other allied health professionals if it was deemed necessary. Caregiver burden was measured using the ZBI, which uses a scale ranging from 0 to 88, with higher

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scores implying greater perceived burden. The intervention group showed significant reductions in caregiver burden scores from baseline to 1 month (32.8 ± 12.2 vs. 22.0 ± 5.3, $P = 0.002$) and 3 months (21.3 ± 6.6, $P = 0.02$). The intervention group also had significantly lower caregiver burden compared to the control group at 1 month (22.0 ± 5.3 vs. 31.6 ± 9.5, $P = 0.006$) and 3 months (21.3 ± 6.6 vs. 33.4 ± 7.2, $P = 0.009$).

Education-only Interventions

A study conducted in India evaluated the effect of an information booklet for caregivers of patients on hemodialysis on their knowledge of home care management using a pre-post-test study design [53]. Caregivers ($n = 30$) were provided with a booklet which was developed from a literature review and expert input. The post-test assessment was conducted 1 week after receiving the booklet. The major findings showed that there was a significant improvement in overall knowledge scores, from 50.35 in the pre-test to 86.25 post-test. The overall improvement in the mean score was 35–89 ($t = 13.4$, $P < 0.001$).

Tornay [55] conducted a study in Spain using participatory action research, in which an information handbook was developed for the post-transplant care of children. Over an 8-year period, data were collected from children and caregivers through semistructured interviews, clinical histories, and written opinions, and these data were used to develop and modify the information handbook. The handbook included information on diet, immunosuppressive mediation, side effects, protection of the implanted organ, signs of rejection, and self-care. The handbook was distributed to pediatric transplant recipients ($n = 135$) aged from 2 to 18 years old from immediately post-transplant up to 7 years post-transplant, and to their caregivers. Evaluation of the handbook found that over 90% of the patients and caregivers felt that it helped reduce distress and fear, adapt to life post-transplant and improve the patient's self-care.

Patient and Caregiver Needs and Preferences

Currently, there are no studies evaluating patient and caregiver preferences for interventions or outcomes specifically regarding family and caregiver support. Further research that elicits and evaluates caregiver needs and preferences is needed to validate the areas that have already been identified, such as depression, stress, fatigue, isolation, and ability to cope, and to identify other topics and outcomes of importance to caregivers. This knowledge can then be used to develop interventions which target the needs and priorities of caregivers to reduce caregiver burden, improve caregiver support, and ultimately improve patient and caregiver health outcomes.

Conclusion

The problems and challenges of caregiving can impair quality of life and impact on caregivers and patient health and outcomes. However, high-quality evidence on effects of interventions to support caregivers remains very limited and consists of randomized controlled studies, participatory action research, and pre- and post-test studies. Studies focus on educational and psychosocial interventions to improve caregiver knowledge, burden, and quality of life. No studies addressed practical support as the intervention. Further research on a range of interventions targeting mental health, and social and practical support is needed. Family-based therapies may also have potential to alleviate caregiver burden and improve outcomes. As recommended by the World Health Organization and UK INVOLVE, we suggest involving caregivers in the decision-making, planning, implementation, and evaluation of interventions that impact their health and their capacity to provide care for their loved ones.

Support for caregivers of patients with CKD is critical. Patient-centered care incorporates the need to support informal caregivers in their caregiving role to ensure that patients and their caregivers have the best possible outcomes.

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