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can be performed by convective clearance (continuous venovenous hemofiltration [CVVH]), in which large volumes of plasma water (and accompanying solutes) are forced across the semipermeable membrane by means of hydrostatic pressure; the plasma water is then replaced by a physiologic crystalloid solution. CRRT can also be performed by dif fusive clearance (continuous venovenous hemodialysis [CVVHD]), a technology similar to hemodialysis except at lower blood flow and dialy sate flow rates. A hybrid therapy combines both diffusive and convective clearance (continuous venovenous hemodiafiltration [CVVHDF]). To achieve some of the advantages of CRRT without the need for 24-h staffing of the procedure, some physicians favor slow low-efficiency dialysis (SLED) or extended daily dialysis (EDD). In this therapy, blood flow and dialysate flow are higher than in CVVHD, but the treatment time is reduced to ≤12 h. The choice of modality is often dictated by the immediate availability of technology and the expertise of medical staff. The optimal dose of dialysis for AKI for any particular patient is not clear. Daily intermittent hemodialysis and high-dose CRRT do not confer a demonstrable survival or renal recovery advantage, but care should be taken to avoid undertreatment. Studies have failed to show that continuous therapies are superior to intermittent therapies when measuring survival rates. If available, CRRT is often preferred in patients with severe hemodynamic instability, cerebral edema, or significant volume overload. Peritoneal dialysis can be performed through a temporary intra peritoneal catheter. It is rarely used in the United States for AKI in adults (although it was “rediscovered” during the COVID-19 pandemic owing to inadequate numbers of continuous and intermittent hemo dialysis machines). Peritoneal dialysis has enjoyed widespread use internationally, particularly when hemodialysis technology is not as readily available. Dialysate solution is instilled into and removed from the peritoneal cavity at regular intervals in order to achieve diffusive and convective clearance of solutes across the peritoneal membrane; ultrafiltration of water is achieved by the presence of an osmotic gradi ent across the peritoneal membrane achieved by high concentrations of dextrose in the dialysate solution. Because of its continuous nature, it is often better tolerated than intermittent procedures like hemodialysis in hypotensive patients. Peritoneal dialysis may not be sufficient for hypercatabolic patients due to inherent limitations in dialysis efficacy. OUTCOME AND PROGNOSIS The development of AKI is associated with a significantly increased risk of in-hospital and long-term mortality, longer length of stay, and increased costs. AKI is also associated with an increased risk of later cardiovascular disease events, though the mechanisms are not well understood. Prerenal azotemia, with the exception of the cardiorenal and hepatorenal syndromes, and postrenal azotemia carry a better prognosis than most cases of intrinsic AKI. The kidneys may recover even after severe, dialysis-requiring AKI. Survivors of an episode of AKI requiring temporary dialysis, however, are at extremely high risk for progressive CKD, and up to 10% may develop ESKD requiring dialysis or transplantation. AKI and CKD are increasingly seen as interrelated syndromes: CKD is a major risk factor for the development of AKI, and AKI is a risk factor for the future development of CKD. Measurement of albuminuria after an AKI episode can help predict the risk of kidney disease progression and can serve as a valuable risk-stratification tool. Postdischarge care after AKI under the supervision of a nephrologist for aggressive secondary prevention of kidney disease is prudent. ■ ■FURTHER READING Chawla LS et al: Acute kidney injury and chronic kidney disease as interconnected syndromes. N Engl J Med 371:58, 2014. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group: KDIGO Clinical Practice Guidelines for Acute Kidney Injury. Kidney Int Supp 2:1, 2012. Lake BB et al: An atlas of healthy and injured cell states and niches in the human kidney. Nature 610:585, 2023. Molitoris BA: Low-flow acute kidney injury: The pathophysiology of prerenal azotemia, abdominal compartment syndrome, and obstruc tive uropathy. Clin J Am Soc Nephrol 17:1039, 2022.

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Chronic Kidney Disease CHAPTER 322 Chronic kidney disease (CKD) encompasses a spectrum of pathophysi ologic processes associated with abnormal kidney function, often with a progressive decline in glomerular filtration rate (GFR). The risk of worsening CKD is closely linked to the GFR, its trajectory over time, and the quantity of urinary albumin excretion (albuminuria). Figure 322-1 provides a staging of CKD stratified by the estimated risk for further progressive decline of GFR based on these parameters. Chronic Kidney Disease The dispiriting term end-stage renal disease represents a stage of CKD where the accumulation of toxins, fluid, and electrolytes nor mally excreted by the kidneys leads to death unless the toxins are removed by renal replacement therapy by means of dialysis or kidney transplantation. These interventions are discussed in Chaps. 323 and 325. End-stage renal disease will be supplanted in this chapter by the term stage 5 CKD. ■ ■PATHOPHYSIOLOGY OF CKD The pathophysiology of CKD involves two broad mechanisms of dam age: (1) specific initiating mechanisms particular to the underlying etiology (e.g., genetic abnormalities in development, immune complex deposition, inflammation, metabolic, microvascular perturbation, or toxin exposure affecting vascular, glomerular, or tubulointerstitial compartments of the kidney), and (2) nonspecific mechanisms involv ing hyperfiltration and hypertrophy of the remaining viable nephrons, which are common consequences of long-term reduction of renal mass, irrespective of underlying etiology. The responses to reduction in nephron number are mediated by vasoactive hormones, cytokines, and growth factors. Eventually, the short-term adaptations of hyper filtration and hypertrophy to maintain GFR become maladaptive as the increased pressure and flow within the nephron predisposes to distortion of glomerular architecture, abnormal podocyte function, and disruption of the filtration barrier, leading to sclerosis and dropout of the remaining nephrons. Increased intrarenal activity of the reninangiotensin system (RAS) together with reduced tubuloglomerular feedback appears to contribute both to the initial compensatory hyper filtration and to the subsequent maladaptive hypertrophy and sclerosis (Fig. 322-2). This process explains why a reduction in functioning nephron number from initial injuries may lead to a progressive decline in kidney function over many years. ■ ■IDENTIFICATION OF RISK FACTORS AND STAGING OF CKD There has been significant progress in the identification of risk factors that increase the risk for CKD, even in individuals with normal GFR and often years prior to the development of overt kidney impairment (Table 322-1).

PART 9 Disorders of the Kidney and Urinary Tract <10 urine alb/cr (mg/g) 10–29 urine alb/cr (mg/g) 30–299 urine alb/cr (mg/g) 300–999 urine alb/cr (mg/g)

> 1000 urine alb/cr (mg/g)

Relative Risk (RR) All-Cause Mortality by GFR and Proteinuria

> 105 90–104 60–89 45–59 30–44 15–29 <15 Glomerular Filtration Rate (mL/min/1.73 m2) A

Relative Risk (RR) Cardiovascular Mortality by GFR and Proteinuria

> 105 90–104 60–89 45–59 30–44 15–29 <15 B Kidney Failure with Replacement Therapy by GFR and Proteinuria 105 90–104 60–89 45–59 30–44 15–29 <15 C FIGURE 322-1 Kidney Disease Improving Global Outcome (KDIGO) classification of chronic kidney disease (CKD). Glomerular filtration rate (GFR) and Increasing albuminuria correspond to increasing risk of All-Cause Mortality (A), Cardiovascular Mortality (B) and Progression of CKD (C). (Figure created using data from ME Grams et al: JAMA 330:1266, 2023.) Adults with such risk factors should be monitored yearly for urinary albumin excretion level, decline in estimated GFR (eGFR), and blood pressure, so that a clinical reno-protective management pathway can be planned. More recently, identified risk factors for which there is now a consensus include tobacco use, increased body mass index (BMI) and sedentary lifestyle, a past episode of clinically recovered acute kidney injury (AKI), and many forms of apparently recovered childhood and adolescent kidney disease. There is also an increasing awareness of the role of genetic risk fac tors, which may account for up to 20% of adult-onset CKD, depending on the clinical phenotype, family background, demographic history, and population

ancestry. Many rare inherited forms of CKD follow a Mendelian inheritance pattern, sometimes as part of a systemic syndrome, with the most common in this category being autosomal dominant polycystic kidney disease (ADPKD). In addition, it is now appreciated that many unique, kindred-specific, site-specific copy number variants and microdeletions, as well as functional single nucleotide variants at >300 genetic loci known to harbor systemic and kidney-only disease pathogenic mutations with high penetrance, also contribute to pleiotropic presentations of CKD (Table 322-2). Many of the genes with identified CKD-causing mutations are expressed in the podocytes of the glomeruli or in the glomerular basement membrane, but others are expressed in tubule segments associated with a primary tubulointerstitial process and secondary glomerular injury. In addition to these high penetrance mutations, DNA sequence variants with partial penetrance for causation or progression of CKD have been identified and often require an acquired second hit for emer gence of disease. A striking example is the finding of allelic versions of the APOL1 gene, of sub-Saharan African population ancestry, which contributes to the several-fold higher frequency of certain common

Distal tubule Distal tubule Afferent arteriole Efferent arteriole Normal kidney Glomerulus Tubule Tubule A B FIGURE 322-2 Schematic representation of the effect of intraglomerular hypertension on nephron survival. etiologies of nondiabetic CKD (e.g., focal segmental glomerulosclе rosis, HIV- and SARS-CoV-2–associated nephropathy, CKD with hypertension, lupus nephritis) observed among African and Hispanic Americans in major regions of continental Africa and the global African diaspora. The prevalence in West African populations seems to have arisen as an evolutionary adaptation conferring protection from tropi cal pathogens. As in other common diseases with a heritable compo nent, acquired triggers (e.g., increased levels of interferon-γ and other cytokines) can transform genetic risk into disease. In addition to these single-gene loci, recent studies have identified genome-wide patterns of DNA sequence variants that confer increased risk for CKD. These include risk alleles associated with idiopathic IgA and idiopathic mem branous glomerulopathy. Staging of CKD (Fig. 322-1) is based on both GFR and on urinary albumin excretion rate and is key to understanding the emergence of symptoms, for determining the risk and rate of CKD progression and complications, and for determining indications for medical interven tion. GFR is estimated (eGFR) rather than directly measured, using equations that include serum creatinine concentration and various other individual patient parameters, in place of timed urine collections, which have proven cumbersome and unreliable. U.S.-based national professional societies have recommended utilizing the equations shown in Table 322-3. eGFR determination in CKD is valid only if the patient is in steady state, that is, the serum creatinine is neither rising nor falling over days. The newly recommended equations no longer include a parameter that adjusts for differences in creatinine produc tion based on continental ancestry (race-free eGFR estimation equa tions). However, in some situations where precise estimation of GFR might affect medication dosing or other individual clinical decisions, it is reasonable to include an estimated adjustment based on various parameters that could modify creatinine production downward (e.g., loss of a limb) or upward (increased muscle mass) or, in some cases, revert to measure timed creatinine production rates or use of the more costly and less widely available marker cystatin-C, which is not affected by variables that influence creatinine production. The normal annual mean decline in GFR with age from the peak GFR (~120 mL/min per 1.73 m2) attained during the third decade of

Urinary protein Efferent arteriolar constricted Afferent arteriole Ang II Ang II Increased intraglomerular pressure CHAPTER 322 Chronic Kidney Disease life is ~1 mL/min per year per 1.73 m2, reaching a mean value of 70 mL/ min per 1.73 m2 at age 70, with considerable interindividual variability. Although reduced GFR is expected with aging, the lower GFR signifies a true loss of kidney function with attendant consequences in terms of risk of CKD complications and requirement for dose adjustment of medications. The mean GFR is lower in women than in men, though men are at greater risk for CKD than women. A woman in her eight ies with a laboratory report of serum creatinine in the normal range may have a GFR of <50 mL/min per 1.73 m2. Relatedly, even a mild elevation in serum creatinine concentration often signifies a substantial reduction in GFR in older individuals. It is not entirely clear as yet as to whether advancing age as a risk factor for progressive CKD is indepen dent of such age-related reduction in the measure of eGFR. Measurement of albuminuria is also helpful for monitoring nephron injury and the response to therapy in many forms of CKD, especially chronic glomerular diseases. The cumbersome 24-h urine collection has been replaced by measurement of urinary albumin-to-creatinine ratio (UACR) in one and preferably several spot first-morning urine samples as a measure pointing to glomerular injury. Even in patients with negative conventional urinary dipstick tests for protein, persis tent UACR >2.5 mg/mmol (male) or >3.5 mg/mmol (female) on two to three occasions serves as a marker not only for early detection of primary kidney disease but for systemic microvascular disease as well. A Kidney Failure Risk (KFR) equation has been devised to predict the risk of progression to stage 5 dialysis-dependent kidney disease. The equa tion is available on many sites online (for example, www.kidneyfailurerisk. com) and uses age, sex, region (North American or non–North American), GFR, and UACR. It has been validated in several cohorts around the world, although the risk for progression appears to be greater in North America, accounting for the regional adjustment in the equation. Stages 1 and 2 CKD are usually asymptomatic, such that the recog nition of CKD occurs more often as a result of laboratory testing in clinical settings other than suspicion of kidney disease. Moreover, in the absence of the risk factors noted above, population-wide screening is not recommended. With progression to CKD stages 3 and 4, clinical and laboratory complications become more prominent. Virtually all organ systems are affected, but the most evident complications include

TABLE 322-1 Risk Factors for Chronic Kidney Disease (CKD)a Noncommunicable Diseases Diabetes Increased BMI Autoinflammatory disease (e.g., lupus, vasculitis, cancer immunotherapy) Nephrotoxic exposure (including many antineoplastic therapies) Hypertension (risk, cause, or consequence) Communicable Diseases Streptococcal infection Mycobacterial infection HIV infection (HIVAN) SARS-CoV-2 HBV, HCV Demographic, Anthropomorphic, Ancestry, Geographic Age Male sex Population ancestry Region-specific CKD risk of uncertain etiology (e.g., Central America, Sri Lanka, and indigenous peoples of Australia and New Zealand) Family history of kidney disease Genetic Monogenic inheritance with (1) high penetrance or (2) low to medium PART 9 Disorders of the Kidney and Urinary Tract penetrance Polygenic risk factors Childhood-Related Risk Factors Premature and SGA birth Persistent asymptomatic microscopic hematuria Childhood kidney disease (even resolved) Treated childhood cancer Lifestyle Tobacco use Sedentary lifestyle Other Prior acute kidney injury Preeclampsia Kidney donation (or other acquired nephrectomy) aNot biomarkers. Abbreviations: BMI, body mass index; HBV, hepatitis B virus; HCV, hepatitis C virus;

HIVAN, HIV-associated nephropathy; SGA, small for gestational age. anemia with easy fatigability; decreased appetite with progressive malnutrition; abnormalities in calcium, phosphorus, and mineralregulating hormones, such as 1,25(OH)2D3 (calcitriol), parathyroid hormone (PTH), and fibroblast growth factor 23 (FGF-23); and abnor malities in sodium, potassium, water, and acid-base homeostasis. Many patients, especially older individuals, will have eGFR values compatible with stage 2 or 3 CKD. However, the majority of these patients will show no further deterioration of kidney function. In this setting, it is advised to recheck kidney function, and if it is stable and not associ ated with proteinuria, the patient can usually be followed with interval repeat testing without referral to a nephrologist. If repeat testing shows declining GFR, albuminuria, or uncontrolled hypertension, referral to a nephrologist is appropriate. If the patient progresses to stage 5 CKD (GFR <15 mL/min), toxins accumulate such that patients usually experience a disturbance in their activities of daily living, well-being, nutritional status, and water and electrolyte homeostasis, eventuating in the uremic syndrome. ■ ■ETIOLOGY AND EPIDEMIOLOGY It has been estimated from population data that at least 6% of the adult population in the United States has CKD at stages 1 and 2. An additional 4.5% of the U.S. population is estimated to have stages 3 and 4 CKD. Table 322-4 lists the five most frequent clinical catego ries of CKD, cumulatively accounting for >90% of the CKD disease burden worldwide. The relative contribution of each category varies among different geographic regions. The most frequent cause of CKD

TABLE 322-2 Monogenic Risk Loci for Chronic Kidney Disease (CKD) Copy Number Variants Causative of Congenital Renal Anomalies 1q21 4p16.1-p16.3 16p11.2 16p13.11 17q12 22q11.2 Five Most Predominant Causes of CKD with Mendelian Inheritance Genes for autosomal dominant polycystic kidney disease ADPKD1 ADPKD2 IFT140 GANAB DNAJB2 ALG9 Genes for type IV collagen-associated nephropathy COL4A3 COL4A4 COL4A5 Genes for autosomal dominant tubulointerstitial kidney disease UMOD MUC1 HNF1B Genes for nephronophthisis NPHP genes Other Genes with known common variants that confer increased risk with odds ratio exceeding 2 with non-Mendelian inheritance patterns APOL1 in North America and Europe is diabetic nephropathy, most often secondary to type 2 diabetes mellitus. Patients with newly diagnosed CKD often have hypertension. When no overt evidence for a primary glomerular or tubulointerstitial kidney disease process is present, CKD is frequently attributed to hypertension. However, it is now appreciated that some of these patients may have a subclinical primary glomeru lopathy, such as focal segmental or global glomerulosclerosis, and the elevated blood pressure is a consequence of the kidney disease. In other patients, progressive nephrosclerosis and hypertension are the renal correlates of a systemic vascular disease, often also involving large and small vessels elsewhere, such as the heart and brain. This latter combi nation is especially common in older patients, among whom chronic kidney ischemia as a cause of CKD may be underdiagnosed. ■ ■PATHOPHYSIOLOGY AND BIOCHEMISTRY

OF UREMIA Uremia is the syndrome with symptoms, signs, and accompanying dis turbances in laboratory measurements that result from reduced kidney TABLE 322-3 Recommended Equations for Estimation of Glomerular Filtration Rate (GFR) Using Serum Creatinine Concentration (SCr), Age, Sex, Race, and Body Weight

1. Equation from the Modification of Diet in Renal Disease Study Estimated GFR (mL/min per 1.73 m2) = 1.86 × (SCr)−1.154 × (age)−0.203 Multiply by 0.742 for women Multiply by 1.21 for African ancestry (currently under review)

2. CKD-EPI Equation GFR = 141 × min(SCr/kappa, 1)α × max(SCr/kappa, 1)–1.209 × 0.993Age Multiply by 1.018 for women Multiply by 1.159 for African ancestry (currently under review) where SCr is serum creatinine in mg/dL, kappa is 0.7 for females and 0.9 for males, α is –0.329 for females and –0.411 for males, min indicates the minimum of SCr/kappa or 1, and max indicates the maximum of SCr/kappa or 1. Abbreviation: CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration.

TABLE 322-4 Leading Categories of Etiologies of Chronic Kidney Disease (CKD)a • Diabetic nephropathy • Glomerulonephritis • Hypertension-associated CKD (includes vascular and ischemic kidney disease and primary glomerular disease with associated hypertension) • Autosomal dominant polycystic kidney disease • Other cystic and tubulointerstitial nephropathy aRelative contribution of each category varies with geographic region and race. function. Although serum urea and creatinine concentrations rise with reduced excretory capacity of the kidneys, accumulation of these two molecules themselves does not account for the symptoms and signs that characterize the uremic syndrome. Large numbers of solutes that accumulate when GFR declines have been implicated. These include water-soluble, hydrophobic, protein-bound, charged, and uncharged nitrogen-containing nonvolatile products of metabolism. It is thus evident that the serum concentrations of urea and creatinine should be viewed as being readily measured but very incomplete surrogate markers for retained toxins, and monitoring the levels of urea and cre atinine in the patient with impaired kidney function represents a vast oversimplification of the uremic state. The uremic syndrome involves more than renal excretory failure. A host of metabolic and endocrine functions normally performed by the kidneys are also impaired and can result in anemia, malnutrition, and abnormal metabolism of carbohydrates, fats, and proteins. Fur thermore, plasma levels of many hormones, including PTH, FGF-23, insulin, glucagon, steroid hormones including vitamin D and sex hormones, and prolactin change with CKD as a result of reduced excre tion, decreased degradation, or abnormal regulation. Finally, CKD is associated with increased systemic inflammation. Elevated levels of C-reactive protein are detected along with other acute-phase reactants, whereas levels of so-called negative acute-phase reactants, such as albu min and fetuin, decline. Thus, the inflammation associated with CKD is important in the malnutrition-inflammation-atherosclerosis/calcifi cation syndrome, which contributes in turn to the acceleration of vas cular disease and morbidity associated with advanced kidney disease. In summary, the pathophysiology of the uremic syndrome can be divided into manifestations in three spheres of dysfunction: (1) those consequent to the accumulation of toxins that normally undergo renal excretion; (2) those consequent to the loss of other kidney functions, such as fluid and electrolyte homeostasis and hormone regulation; and (3) progressive systemic inflammation and its vascular and nutritional consequences. CLINICAL AND LABORATORY MANIFESTATIONS OF CKD AND UREMIA ■ ■FLUID, ELECTROLYTE, AND ACID-BASE DISORDERS Sodium and Water Homeostasis With normal kidney function, excretion of filtered sodium and water matches intake. Many forms of kidney disease disrupt this balance such that dietary intake of sodium exceeds its excretion, leading to sodium retention and attendant extra cellular fluid volume (ECFV) expansion. This expansion may contrib ute to hypertension, which itself can accelerate nephron hyperfiltration and injury. As long as water intake does not exceed the capacity for renal water clearance, the ECFV expansion will be isonatric and the patient will have a normal plasma sodium concentration. Hyponatre mia is not commonly seen in CKD patients, but when present, often responds to water restriction. The patient with ECFV expansion should be counseled regarding salt restriction. While the thiazide diuretic chlorthalidone alone has been shown to reduce elevated blood pressure in some patients even with stage 4 CKD, administration of loop diuret ics, including furosemide, bumetanide, or torsemide, may be needed to manage sodium accumulation. Resistance to loop diuretics in CKD often mandates use of higher doses than those used in patients with

normal GFR. The combination of loop diuretics with metolazone may be helpful. Diuretic resistance with intractable edema and hypertension in advanced CKD may serve as an indication to initiate dialysis.

Rarely, patients with CKD may have impaired renal conservation of sodium and water. When an extrarenal cause for fluid loss, such as gastrointestinal (GI) loss, is present, these patients may be prone to ECFV depletion because of the inability of the failing kidney to reclaim filtered sodium adequately. Any depletion of ECFV, whether due to GI losses, renal sodium loss, or overzealous diuretic therapy, can further compromise kidney function through hypoperfusion, or a “prerenal” state, leading to acute-on-chronic kidney failure. In this setting, holding or adjusting the diuretic dose or rarely even cautious volume repletion with normal saline may return the ECFV to normal and restore renal function to baseline. Many patients are given a “sick day” warning, wherein should they experience volume depletion, for example from vomiting or diarrhea, they are told to not take their diuretics or other antihypertensive medications until they resume eat ing and drinking normally. Potassium Homeostasis In CKD, the decline in GFR is not necessarily accompanied by a parallel decline in urinary potassium excretion, which is predominantly mediated by aldosterone-dependent secretion in the distal nephron. Another defense against potassium retention in these patients is augmented potassium excretion in the GI tract. Notwithstanding these two homeostatic responses, hyperkalemia may be precipitated in certain settings. These include increased dietary potassium intake, hemolysis, transfusion of stored red blood cells, and metabolic acidosis. Importantly, a host of medications can inhibit renal potassium excretion and lead to hyperkalemia. The most important medications in this respect include the RAS inhibitors and spirono lactone and other potassium-sparing diuretics such as amiloride, eplerenone, and triamterene, as well as the new nonsteroidal miner alocorticoid receptor antagonists. As will be outlined below, several of these are major agents in the medical management armamentarium to slow or prevent progression of CKD. The benefits of the RAS inhibitors in ameliorating hyperfiltration and progression of CKD and mitigating cardiovascular complications very often favor their cautious and judi cious use with very close monitoring of plasma potassium concentra tion. Coadministration of potassium-lowering agents may allow for the use of RAS inhibitors with reduced risk of hyperkalemia. Gratifyingly, the gliflozin diuretics, administrated even in advanced stages of CKD, seem to have counterbalancing effects on kidney potassium handling that result in net preservation of potassium homeostasis. CHAPTER 322 Chronic Kidney Disease Certain causes of CKD can be associated with earlier and more severe disruption of potassium secretory mechanisms in the distal nephron, out of proportion to the decline in GFR. These include con ditions associated with hyporeninemic hypoaldosteronism, such as diabetes, and renal diseases that preferentially affect the distal nephron, such as obstructive uropathy and sickle cell nephropathy. Hypokalemia is not common in CKD and usually reflects markedly reduced dietary potassium intake, especially in association with exces sive diuretic therapy or concurrent GI losses. The use of potassium supplements and potassium-sparing diuretics may be risky in patients with impaired renal function and needs to be monitored closely. Metabolic Acidosis Metabolic acidosis is a common disturbance in CKD. The majority of patients can still acidify the urine, but they produce less ammonia and, therefore, cannot excrete the quantity of protons required to maintain acid-base balance in most diets. Hyperkalemia, if present, further depresses ammonia production. The combination of hyperkalemia and hyperchloremic metabolic acidosis is often present, even at earlier stages of CKD, in patients with diabetic nephropathy or in those with predominant tubulointerstitial disease including obstructive uropathy. With further declining GFR, the total urinary net daily acid excretion may be severely limited to <30–40 mmol, and the accumulation of anions of retained organic acids can then lead to an anion-gap metabolic acidosis. Thus, the non-anion-gap metabolic acidosis seen in earlier stages of CKD may be complicated by the addition of an anion-gap metabolic acidosis as CKD progresses. In most patients, the metabolic acidosis is mild; the pH is rarely <7.32

and can usually be corrected with oral sodium bicarbonate supplemen tation. Studies have suggested that even modest degrees of metabolic acidosis may be associated with the development of protein catabolism and progression of CKD.

TREATMENT Fluid, Electrolyte, and Acid-Base Disorders Dietary salt restriction and the use of loop diuretics, occasion ally in combination with metolazone, may be needed to main tain euvolemia. Water restriction is indicated only if there is hyponatremia. Hyperkalemia often responds to dietary restriction of potassium, the use of kaliuretic diuretics, and both avoidance of potassium supplements (including occult sources, such as dietary salt substi tutes) and monitoring with dose adjustment, or at times avoidance of potassium-retaining medications, which are often prescribed to slow CKD progression or afford cardioprotection (RAS inhibitors, steroidal or nonsteroidal mineralocorticoid antagonists). Kaliuretic diuretics promote urinary potassium excretion, whereas potassiumbinding resins, such as calcium resonium, sodium polystyrene, or the newer agents patiromer and calcium zirconium cyclosilicate, promote potassium loss through the GI tract and may reduce the incidence of hyperkalemia. Intractable hyperkalemia is an indica tion (although uncommon) to consider institution of dialysis in a CKD patient. The renal tubular acidosis and subsequent anion-gap metabolic acidosis in progressive CKD will respond to alkali sup plementation. Recent studies suggest that this replacement should be considered when the serum bicarbonate concentration falls below 20–23 mmol/L to avoid the protein catabolic state seen with even mild degrees of metabolic acidosis. Relatedly, a recent study suggested that bicarbonate supplementation in stages 3–5 CKD was also associated with slower progression to dialysis. The sodium load in sodium bicarbonate supplementation needs to be taken into account when ECFV expansion is present. PART 9 Disorders of the Kidney and Urinary Tract ■ ■DISORDERS OF CALCIUM AND PHOSPHATE METABOLISM The principal complications of abnormalities of calcium and phosphate metabolism in CKD occur in the skeleton and the vascular bed, with occasional involvement of soft tissues. It is likely that disorders of bone turnover and disorders of vascular and soft tissue calcification are related to each other. Bone Manifestations of CKD The major disorders of bone disease can be classified into those associated with high bone turn over with increased PTH levels (including osteitis fibrosa cystica, the classic lesion of secondary hyperparathyroidism), osteomalacia due to reduced vitamin D effect, and low bone turnover with low or normal PTH levels (adynamic bone disease) or often some combination of the foregoing. The pathophysiology of secondary hyperparathyroidism and the consequent high-turnover bone disease is related to abnormal mineral metabolism through the following series of interrelated mechanisms: (1) declining GFR leads to reduced excretion of phosphate and, thus, phosphate retention; (2) the retained phosphate stimulates increased synthesis of both FGF-23 by osteocytes and of PTH and also stimulates growth of parathyroid gland mass; and (3) decreased levels of ionized calcium, which results from decreased levels of renal calcitriol produc tion due to phosphate retention and elevated levels of FGF-23, which also increases degradation of calcitriol. Low calcitriol levels contribute to hyperparathyroidism, both by leading to hypocalcemia and also by a direct effect on PTH gene transcription. In addition, the normal inhibi tory effect of FGF-23 on PTH production, which is Klotho-dependent, is also attenuated in CKD. These changes start to occur when the GFR falls below 60 mL/min, though some studies point to retention of phos phate as an event antedating measurable reduction in GFR, together with early elevation of FGF-23 as well. FGF-23 is part of a family of

phosphatonins that promotes phosphate excretion, and high levels of FGF-23 are an independent risk factor for left ventricular hypertrophy and are associated with increased mortality in CKD, dialysis, and kid ney transplant patients. Hyperparathyroidism stimulates bone turnover and leads to oste itis fibrosa cystica. Bone histology shows abnormal osteoid, bone and bone marrow fibrosis, and, in advanced stages, the formation of bone cysts, sometimes with hemorrhagic elements so that they appear brown in color; hence, the term brown tumor. Clinical manifestations of severe hyperparathyroidism include bone pain and fragility, brown tumors with compression syndromes, and resistance to erythropoiesisstimulating agents (ESA) in part related to the bone marrow fibrosis. Furthermore, PTH itself is considered a uremic toxin, and high levels are associated with muscle weakness, fibrosis of cardiac muscle, and constitutional symptoms. Adynamic bone disease is increasing in prevalence, especially among diabetics and older patients. It is characterized by reduced bone volume and mineralization and may result from excessive suppression of PTH production, chronic inflammation, or both. Suppression of PTH can result from the use of vitamin D preparations or from exces sive calcium exposure in the form of calcium-containing phosphate binders or high-calcium dialysis solutions. Complications of adynamic bone disease include an increased incidence of fracture and bone pain and an association with increased vascular and cardiac calcification. Occasionally, the calcium will precipitate in the soft tissues into large concretions termed tumoral calcinosis (Fig. 322-3). Patients with adynamic bone disease often experience the most severe symptoms of musculoskeletal pain, owing to the inability to repair the microfractures that occur normally as a part of healthy skeletal homeostasis with regular physical activity. Patients with advanced CKD experience more frequent fractures than their age-matched controls. Osteomalacia is a distinct process, conse quent to reduced production and action of 1,25(OH)2D3, leading to accumulation of nonmineralized osteoid. Calcium, Phosphorus, and the Cardiovascular System There is a strong association between hyperphosphatemia and increased car diovascular mortality in patients with CKD. Hyperphosphatemia and hypercalcemia are associated with increased vascular calcification, but it is unclear whether the excessive mortality is mediated by this mecha nism. Studies using computed tomography (CT) and electron-beam CT scanning show that CKD patients have calcification in the media of coronary arteries and heart valves that appears to be orders of magni tude greater than that in patients without kidney disease. The magni tude of the calcification is proportional to age and hyperphosphatemia and is also associated with low PTH levels and low bone turnover. It is possible, that in CKD patients, ingested calcium cannot be incor porated into bones with low turnover, and therefore, is deposited at FIGURE 322-3 Tumoral calcinosis. This patient was on hemodialysis for many years and was nonadherent to dietary phosphorus restriction or the use of phosphate binders. He was chronically severely hyperphosphatemic. He developed an enlarging painful mass on his arm that was extensively calcified.

FIGURE 322-4 Calciphylaxis. This peritoneal dialysis patient was on chronic warfarin therapy for atrial fibrillation. She noticed a small painful nodule on the abdomen that was followed by progressive skin necrosis and ulceration of the anterior abdominal wall. She was treated with hyperbaric oxygen, intravenous thiosulfate, and discontinuation of warfarin, with slow resolution of the ulceration. extraosseous sites, such as the vascular bed and soft tissues. There is a similar association between osteoporosis and vascular calcification in the general population. Finally, hyperphosphatemia can induce a change in gene expression in vascular cells to an osteoblast-like profile, leading to vascular calcification and even ossification. Other Complications of Abnormal Mineral Metabolism Cal ciphylaxis is a devastating condition seen almost exclusively in patients with advanced CKD. It is heralded by painful livedo reticularis and subcutaneous nodules that advance to patches of ischemic necrosis, especially on the legs, thighs, abdomen, and breasts (Fig. 322-4). Pathologically, there is evidence of vascular occlusion in association with extensive vascular and soft tissue calcification. It appears that this condition is increasing in incidence. Originally it was ascribed to severe abnormalities in calcium and phosphorus control in dialysis patients, usually associated with advanced hyperparathyroidism. How ever, more recently, calciphylaxis has been seen with increasing fre quency in the absence of severe hyperparathyroidism. Warfarin is still used in some CKD patients in whom several members of the direct oral anticoagulant (DOAC) family of drugs are contraindicated, and one of the effects of warfarin therapy is to decrease the vitamin K–dependent activation of matrix GLA protein. This latter protein is important in preventing vascular calcification. Thus, warfarin treatment is con sidered a risk factor for calciphylaxis, and if a patient develops this syndrome, this medication should be discontinued and alternative means of anticoagulation should be chosen, depending on the specific underlying indication for anticoagulation. TREATMENT Disorders of Calcium and Phosphate Metabolism The optimal management of secondary hyperparathyroidism and osteitis fibrosa is prevention. Once the parathyroid gland mass is very large, it is difficult to control the disease. Careful attention should be paid to the plasma phosphate concentration in CKD patients, who should be counseled on a low-phosphate diet as well as the appropriate use of phosphate-binding agents, which are taken with meals and complex dietary phosphate to limit its GI absorption. Examples of phosphate binders are calcium acetate and calcium carbonate. A major side effect of calcium-based phosphate binders is calcium accumulation and hypercalcemia, especially in patients with low-turnover bone disease. Sevelamer and lanthanum are non-calcium-containing polymers that also function as phos phate binders; they do not predispose CKD patients to hypercal cemia and may attenuate calcium deposition in the vascular bed.

Tenapanor is a sodium-proton inhibitor that decreases GI phos phate absorption and may be useful to manage hyperphosphatemia in CKD and dialysis patients.

Calcitriol exerts a direct suppressive effect on PTH secretion and also indirectly suppresses PTH secretion by raising the concentra tion of ionized calcium. However, calcitriol therapy may result in hypercalcemia and/or hyperphosphatemia through increased GI absorption of these minerals. Certain analogues of calcitriol are available (e.g., paricalcitol) that suppress PTH secretion with less attendant hypercalcemia. Recognition of the role of the extracellular calcium-sensing receptor has led to the development of calcimimetic agents that enhance the sensitivity of parathyroid cells to the suppressive effect of calcium. This class of drug, which includes cinacalcet and etelcal cetide, produces a dose-dependent reduction in PTH and plasma calcium concentration in some patients. Current National Kidney Foundation Kidney Disease Outcomes Quality Initiative guidelines recommend a target PTH level between 2 and 9 times the upper limit of normal, recognizing that very low PTH levels are associated with adynamic bone disease and possible consequences of fracture and ectopic calcification. For CKD patients requiring anticoagulation, careful assessment of the indication and choice and dosing of medication appropriate for reduced renal clearance, with avoidance of warfarin, should be considered to reduce the risk of calciphylaxis. CHAPTER 322 ■ ■CARDIOVASCULAR ABNORMALITIES Cardiovascular disease is the leading cause of morbidity and mortality in patients at every stage of CKD. The incremental risk of cardiovascu lar disease in those with CKD compared to the age- and sex-matched general population ranges from 10- to 200-fold, depending on the stage of CKD. As a result, most patients with CKD succumb to cardiovascu lar disease before ever reaching stage 5 CKD. Between 30 and 45% of those patients who do reach stage 5 CKD have advanced significant cardiovascular complications. Chronic Kidney Disease Vascular Disease The increased prevalence of vascular disease in CKD patients derives from both traditional ("classic") and nontra ditional (CKD-related) risk factors. Traditional risk factors include hypertension, diabetes mellitus, hypervolemia, dyslipidemia, sym pathetic overactivity, and hyperhomocysteinemia. The CKD-related risk factors comprise anemia, hyperphosphatemia, hyperparathyroid ism, increased FGF-23, sleep apnea, and systemic inflammation. The inflammatory state appears to accelerate vascular occlusive disease, and low levels of fetuin may permit more rapid vascular calcification, especially in the face of hyperphosphatemia. Other abnormalities seen in CKD may augment myocardial ischemia, including left ventricular hypertrophy and microvascular disease. It is noteworthy that both high and low ejection fraction congestive heart failure, left ventricular hypertrophy, systemic hypertension, and pulmonary hypertension are no less prominent than coronary ischemia as causes of cardiovascular mortality in patients with advanced stages of CKD. Cardiac troponin levels are frequently elevated in CKD without evidence of acute ischemia. The elevation complicates the diagnosis of acute myocardial infarction in this population. Serial measurements may be needed. Therefore, the trend in levels over the hours after presentation may be more informative than a single, elevated level. Interestingly, consistently elevated levels are an independent prognos tic factor for adverse cardiovascular events. Heart Failure Abnormal cardiac function secondary to myocar dial ischemia, left ventricular hypertrophy, diastolic dysfunction, and frank cardiomyopathy, in combination with salt and water retention, often results in heart failure or even pulmonary edema. Heart failure can occur with preserved (diastolic dysfunction) or reduced (systolic dysfunction) ejection fraction. A form of "low-pressure" pulmonary edema can also occur in advanced CKD, manifesting as shortness of breath and a "bat wing" distribution of alveolar edema fluid on chest x-ray. This finding can occur even in the absence of ECFV overload

and is associated with normal or mildly elevated pulmonary venous pressure. This process has been ascribed to increased permeability of alveolar capillary membranes as a manifestation of the uremic state, and it responds to dialysis. Other CKD-related risk factors, including anemia and sleep apnea, may contribute to the risk of heart failure.

Hypertension and left ventricular hypertrophy are common com plications of CKD. Hypertension usually develops early during the course of CKD and is associated with adverse outcomes, including the development of ventricular hypertrophy and a more rapid loss of renal function. Left ventricular hypertrophy and dilated cardiomyopathy are among the strongest risk factors for cardiovascular morbidity and mortality in patients with CKD and are thought to be related primar ily, but not exclusively, to prolonged hypertension and ECFV overload. In addition, anemia and the placement of an arteriovenous fistula for hemodialysis can generate a high cardiac output state and consequent high-output heart failure. It is important to note that in advanced stages of CKD, the presence of an advanced malnutrition-inflammation state can actually reverse the elevation of classic cardiovascular risk factors such as hypertension and hyperlipidemia and is associated in such patients with reduced left ventricular function, loss of body weight, and a poor prognosis. The use of exogenous ESAs can increase blood pressure and the requirement for antihypertensive drugs. Chronic ECFV overload is also a contributor to hypertension, and improvement in blood pressure can often be seen with the use of dietary sodium restriction and diuret ics, and when refractory, hypertension can serve as an indication of ini tiating renal replacement therapy. Nevertheless, because of activation of the RAS and other disturbances in the balance of vasoconstrictors and vasodilators, some patients remain hypertensive, despite careful attention to ECFV status. PART 9 Disorders of the Kidney and Urinary Tract TREATMENT Cardiovascular Abnormalities MANAGEMENT OF HYPERTENSION The overarching goal of hypertension therapy in CKD is to prevent the extrarenal complications of high blood pressure, such as cardio vascular disease and stroke. National guideline panels recommend that in CKD patients with diabetes or proteinuria >1 g per 24 h, blood pressure should be reduced to <130/80 mmHg, if achiev able without prohibitive adverse effects. Salt restriction should be the first line of therapy. When volume management alone is not sufficient, the choice of antihypertensive agent is similar to that in the general population. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) appear to slow the rate of decline of kidney function in a manner that extends beyond reduction of systemic arterial pressure and that involves reduction in the intraglomerular hyperfiltration and hyperten sion by disproportionately reducing glomerular efferent arteriolar vasoconstriction. Occasionally, introduction of ACE inhibitors and ARBs can actually precipitate an episode of AKI, especially when used in combination in patients with ischemic renovascular disease. More commonly, a slight reduction of GFR (<30% of baseline) may actually signify a salutary reduction in intraglomerular hypertension and hyperfiltration and, if stable over time, can be tolerated with continued monitoring. With progressive CKD, RAS inhibitors can be continued with careful monitoring. Careful clinical studies have shown that even in patients with an eGFR <30 mL/min, continuation of these agents was not associated with any signal for harm compared to those in whom the drugs were stopped and that discontinuing RAS inhibitors in CKD was associated with an increased risk of death or cardiovascular events but a lower incidence of starting kidney replace ment therapy. Since the use of ACE inhibitors and ARBs may also be complicated by the development of hyperkalemia, the concomitant use of kaliuretic diuretics (e.g., furosemide with metolazone) or a potassium-lowering GI tract binder, such as patiromer, can improve potassium excretion in addition to improving blood pressure control. Likewise, if gliflozins are implemented in renoprotection, then these

may also assist in potassium homeostasis. Potassium-sparing diuret ics, such as amiloride and triamterene, should be avoided in most patients, and steroidal (e.g., spironolactone) or nonsteroidal (finere none) mineralocorticoid receptor blockers should be accompanied by careful monitoring of serum potassium concentration, weighing potential cardiovascular and renoprotective benefits against risk for lethal hyperkalemia. The recent movement to even lower blood pressure targets in the general population may not be applicable to patients with CKD, who often lack autoregulation to maintain GFR in the face of low perfusion pressure. If a patient experiences sudden decline in kidney function with intensification of antihypertensive therapy, consideration should be given to reducing therapy. MANAGEMENT OF CARDIOVASCULAR DISEASE

There are many strategies available to treat the traditional and nontraditional risk factors in CKD patients. Although these have proved effective in the general population, there is little evidence for their benefit in patients with the most advanced stages of CKD. Certainly, hypertension and dyslipidemia promote atherosclerotic disease and are treatable complications of CKD. Renal disease complicated by nephrotic syndrome is associated with a very ath erogenic lipid profile and hypercoagulability, which increases the risk of occlusive vascular disease. Because diabetes mellitus and hypertension are frequently associated with advanced CKD, it is not surprising that cardiovascular disease is the most frequent cause of death in dialysis patients. The use of the gliflozins (sodium-glucose cotransporter 2 [SGLT2] inhibitors) in patients with and without diabetes mellitus is quickly becoming a mainstay for both kidney protection, with marked amelioration of GFR reduction, and a reduction in cardiovascular events, including heart failure, even in advanced stages of CKD (including stage 4). Pericardial Disease Chest pain with respiratory accentuation, accompanied by a friction rub, is diagnostic of pericarditis. Classic electrocardiographic abnormalities include PR-interval depression and diffuse ST-segment elevation. Pericarditis can be accompanied by peri cardial effusion that is seen on echocardiography and can rarely lead to tamponade. However, the pericardial effusion can be asymptomatic, and pericarditis can be seen without significant effusion. Pericarditis is observed in advanced uremia and, with the advent of timely initiation of dialysis, is not as common as it once was. It is now more often observed in underdialyzed, nonadherent patients than in those starting dialysis. TREATMENT Pericardial Disease Uremic pericarditis is an absolute indication for the urgent initiation of dialysis or for intensification of the dialysis prescription in those already receiving dialysis. Because of the propensity to hemorrhage in pericardial fluid, hemodialysis should be performed without heparin. A pericardial drainage procedure should be considered in patients with recurrent pericardial effusion, especially with echo cardiographic signs of impending tamponade. Nonuremic causes of pericarditis and effusion include viral, malignant, tuberculous, and autoimmune etiologies. It may also be seen after myocardial infarction and as a complication of treatment with the antihyper tensive drug minoxidil. Consideration could be given to the use of colchicine or nonsteroidal anti-inflammatory drugs, although the latter agents could adversely affect renal function. ■ ■HEMATOLOGIC ABNORMALITIES Anemia A normocytic, normochromic anemia is observed as early as stage 3 CKD and is almost universal by stage 4. The primary cause is insufficient production of erythropoietin (EPO) by the diseased kidneys, together with reduced erythrocyte lifespan and other factors. (See Table 322-5.)

TABLE 322-5 Causes of Anemia in Chronic Kidney Disease Relative deficiency of erythropoietin Diminished red blood cell survival Bleeding diathesis Iron deficiency due to poor dietary absorption and gastrointestinal blood loss Hyperparathyroidism/bone marrow fibrosis Chronic inflammation Folate or vitamin B12 deficiency Hemoglobinopathy Comorbid conditions: hypo-/hyperthyroidism, pregnancy, HIV-associated disease, autoimmune disease, immunosuppressive drugs Causes of Anemia in Chronic Kidney Disease The anemia of CKD is associated with a number of adverse pathophysiologic conse quences, including decreased tissue oxygen delivery and utilization, increased cardiac output, ventricular dilation, and ventricular hyper trophy. Clinical manifestations include fatigue and diminished exercise tolerance, angina, heart failure, decreased cognition and mental acuity, and impaired host defense against infection. In addition, anemia may play a role in growth restriction in children with CKD. Although many studies in CKD patients have found that anemia and resistance to exogenous ESAs are associated with a poor prognosis, the relative con tribution to a poor outcome of the low hematocrit itself, versus inflam mation as a cause of the anemia and ESA resistance, remains unclear. TREATMENT Anemia The availability of recombinant human ESA has been one of the most significant advances in the care of renal patients since the introduction of dialysis and renal transplantation. Its routine use has obviated the need for regular blood transfusions in severely anemic CKD patients, thus dramatically reducing the incidence of transfusion-associated infections, iron overload, and the develop ment of alloantibodies that can sensitize patients to donor kidney antigens and render kidney transplantation more problematic. Adequate bone marrow iron stores should be available before treatment with ESA is initiated. Iron supplementation is usually essential to ensure an optimal response to ESA in patients with CKD because the demand for iron by the marrow frequently exceeds the amount of iron that is immediately available for erythropoiesis (measured by percent transferrin saturation), as well as the amount in iron stores (measured by serum ferritin). For the CKD patient not yet on dialysis or the patient treated with peritoneal dialysis, oral iron supplementation should be attempted. If there is GI intoler ance or poor GI absorption, the patient may have to undergo IV iron infusion, keeping in mind that parenteral iron therapy can increase the susceptibility to bacterial infections and that the adverse effects of free serum iron are still under investigation. In addition to iron, an adequate supply of other major substrates and cofactors for red cell production must be ensured, including vitamin B12 and folate. Anemia resistant to recommended doses of ESA in the face of adequate iron stores may be due to some combination of the fol lowing: acute or chronic inflammation, inadequate dialysis, severe hyperparathyroidism, chronic blood loss or hemolysis, chronic infection, or malignancy. A new class of agents to treat the anemia of CKD are the prolylhydroxylase inhibitors of endogenous hypoxia-inducible factors (HIFs). This inhibition leads to an increase in both endogenous production of EPO and an increase in GI absorption of iron. While studies comparing HIF inhibitors to ESAs have demonstrated simi lar effectiveness, some safety considerations remain to be clarified in the realms of cardiovascular, retinal vessel, and possibly tumor vasculogenesis. Randomized, controlled trials of ESAs in CKD have failed to show an improvement in cardiovascular outcomes with this

therapy. Indeed, there has been an indication that the use of ESAs in CKD may be associated with an increased risk of stroke in those with type 2 diabetes or an increase in thromboembolic events and perhaps a faster progression of renal decline.

Therefore, any benefit in terms of improvement of anemic symp toms needs to be balanced against such potential cardiovascular risk. Since normalization of the hemoglobin concentration has not been demonstrated to be of benefit to CKD patients, current prac tice is to target a hemoglobin concentration of 100–115 g/L. Abnormal Hemostasis Patients with later stages of CKD may have a prolonged bleeding time, decreased activity of platelet factor III, abnormal platelet aggregation and adhesiveness, and impaired pro thrombin consumption. Clinical manifestations include an increased tendency to bleeding and bruising, prolonged bleeding from surgical incisions, menorrhagia, and GI bleeding. Interestingly, CKD patients also have a greater susceptibility to thromboembolism, especially if they have renal disease that includes nephrotic-range proteinuria. The latter condition results in hypoalbuminemia and renal loss of antico agulant factors, which can lead to a thrombophilic state. TREATMENT Abnormal Hemostasis CHAPTER 322 Abnormal bleeding time and coagulopathy in patients with renal failure may be reversed temporarily with desmopressin (DDAVP), cryoprecipitate, IV conjugated estrogens, blood transfusions, and ESA therapy. Rarely with refractory and life-threatening bleeding, tranexamic acid and epsilon aminocaproic acid have also been used for hemostasis control. Optimal dialysis will usually correct a pro longed bleeding time. Chronic Kidney Disease Given the coexistence of bleeding disorders and a propensity to thrombosis that is unique in the CKD patient, decisions about anticoagulation that have a favorable risk-benefit profile in the gen eral population may not be applicable to the patient with advanced CKD. One example is warfarin anticoagulation for atrial fibrillation; the decision to anticoagulate should be made on an individual basis in the CKD patient because there appears to be a greater risk of bleeding complications, as well as the consideration of precipitating calciphylaxis. Certain anticoagulants, such as fractionated low-molecularweight heparin, may need to be avoided or dose-adjusted in these patients, with monitoring of factor Xa activity where available. It is often more prudent to use conventional unfractionated heparin, titrated to the measured partial thromboplastin time, in hospital ized patients requiring an alternative to warfarin anticoagulation. Most of the new classes of oral anticoagulants are eliminated by the kidneys, although apixaban in either full or reduced dose is being used more often in CKD and dialysis patients (Chap. 123). ■ ■NEUROMUSCULAR ABNORMALITIES Central nervous system (CNS), peripheral, and autonomic neuropathy, as well as abnormalities in muscle structure and function, are all wellrecognized complications of CKD. Subtle clinical manifestations of uremic neuromuscular disease usually become evident at stage 3 CKD. Early manifestations of CNS complications include mild distur bances in memory and disturbances in concentration and sleep. Neuromuscular irritability, including hiccups, cramps, and twitching, becomes evident at later stages. In advanced untreated kidney failure, asterixis, myoclonus, seizures, and coma can be seen. Peripheral neuropathy usually becomes clinically evident after the patient reaches stage 4 CKD, although electrophysiologic and histo logic evidence occurs earlier. Initially, sensory nerves are involved more than motor, lower extremities more than upper, and distal parts of the extremities more than proximal. The “restless leg syndrome” is characterized by ill-defined sensations of sometimes debilitating discomfort in the legs and feet relieved by frequent leg movement. Evi dence of peripheral neuropathy without another cause (e.g., diabetes

mellitus or iron deficiency) is an indication for starting renal replace ment therapy. Many of the complications described above will resolve with dialysis, although some may persist.

■ ■GASTROINTESTINAL AND NUTRITIONAL ABNORMALITIES Uremic fetor, a urine-like odor on the breath, derives from the break down of urea to ammonia in saliva and is often associated with an unpleasant metallic taste (dysgeusia). Gastritis, peptic disease, and mucosal ulcerations at any level of the GI tract occur in uremic patients and can lead to abdominal pain, nausea, vomiting, and GI bleeding. These patients are also prone to constipation, which can be worsened by the administration of calcium and iron supplements. The retention of uremic toxins also leads to anorexia, nausea, and vomiting. Protein restriction may be useful to decrease nausea and vomiting; however, it may put the patient at risk for malnutrition and should be carried out, if possible, in consultation with a registered dietitian specializing in the management of CKD patients. Weight loss and protein-energy malnutrition, consequences of low protein and caloric intake, are common in advanced CKD and are often an indication for initiation of renal replacement therapy. Metabolic acidosis and the activation of inflammatory cytokines can promote protein catabolism. A number of indices are useful in nutritional assessment and include dietary history, including food diary, and subjective global assessment; edema-free body weight; and measurement of urinary protein nitrogen appearance. Dual-energy x-ray absorptiometry bioimpedance analysis is now widely used to estimate lean body mass versus fluid weight. Nutritional guidelines for patients with CKD are summarized in the “Treatment” section. PART 9 Disorders of the Kidney and Urinary Tract

■ ■ENDOCRINE-METABOLIC DISTURBANCES Glucose metabolism is impaired in CKD. However, fasting blood glucose is usually normal or only slightly elevated, and mild glucose intolerance does not require specific therapy. Because the kidney contributes to insulin removal from the circulation, plasma levels of insulin are slightly to moderately elevated in most uremic patients, both in the fasting and postprandial states. Because of this diminished renal degradation of insulin, patients on insulin therapy may need progressive reduction in dose as their renal function worsens. Many antihyperglycemic agents, including the gliptins, require dose reduc tion in renal failure, and some, such as metformin and sulfonylureas, are contraindicated when the GFR is less than half of normal. The gliflozins, discussed above, that inhibit sodium-glucose transport in the proximal tubule result in glucose lowering, accompanied by strik ing reductions in kidney function decline and in cardiovascular events. The stabilization of GFR in many patients with this therapeutic inter vention represents a major, important added beneficial effect of these drugs. Their long-term stabilizing effect on GFR and urine albumin excretion appears to result from correction of hyperfiltration early in type 2 diabetes mellitus via reactivation of the tubuloglomerular feed back loop. This represents a fortunate convergence of pathophysiology of glomerular hyperfiltration in diabetes with drug discovery. A similar effect on hyperfiltration by residual nephrons in certain nondiabetic forms of CKD may explain the salutary role of this class of medications more broadly in CKD. Other studies have also pointed to a more direct effect on proximal tubule metabolic pathways that alleviate cell injury. In women with CKD, estrogen levels are low, and menstrual abnor malities, infertility, and inability to carry pregnancies to term are common. When the GFR has declined to ~40 mL/min, pregnancy is associated with a high rate of spontaneous abortion, with only ~20% of pregnancies leading to live births, and pregnancy may hasten the progression of the kidney disease itself. Women with CKD who are contemplating pregnancy should consult first with a nephrologist in conjunction with an obstetrician specializing in high-risk pregnancy. Men with CKD have reduced plasma testosterone levels, and sexual dysfunction and oligospermia may supervene. Sexual maturation may be delayed or impaired in adolescent children with CKD, even among those treated with dialysis. Many of these abnormalities improve or reverse with intensive dialysis or with successful renal transplantation.

■ ■DERMATOLOGIC ABNORMALITIES Abnormalities of the skin are prevalent in progressive CKD. Pruritus is quite common and one of the most vexing manifestations of the uremic state. In advanced CKD, even on dialysis, patients may become more pigmented, and this is felt to reflect the deposition of retained pigmented metabolites, or urochromes. Although many of the cutane ous abnormalities improve with dialysis, pruritus is often tenacious. The first lines of management are to rule out unrelated skin disorders, such as scabies, and to treat hyperphosphatemia, which can cause itch. Local moisturizers, mild topical glucocorticoids, oral antihistamines, and ultraviolet radiation have been reported to be helpful. Agonists of kappa opioid receptors can reduce pruritus intensity and improve quality of life. A skin condition unique to CKD patients called nephrogenic fibros ing dermopathy consists of progressive subcutaneous induration, especially on the arms and legs. The condition is seen very rarely in patients with CKD who have been exposed to the magnetic resonance contrast agent gadolinium. Current recommendations are that patients with CKD stage 3 (GFR 30–59 mL/min) should minimize exposure to gadolinium and those with CKD stages 4–5 (GFR <30 mL/min) should avoid the use of gadolinium agents unless it is medically necessary. However, no patient should be denied an imaging investigation that is critical to management, and under such circumstances, rapid removal of gadolinium by hemodialysis (even in patients not yet receiving renal replacement therapy) shortly after the procedure may mitigate this sometimes devastating complication. Newer forms of gadolinium are not associated with this complication, and it remains to be seen if cau tion about their use will remain relevant. EVALUATION AND MANAGEMENT OF PATIENTS WITH CKD ■ ■INITIAL APPROACH History and Physical Examination Symptoms and overt signs of kidney disease are often subtle or absent until renal failure super venes. Thus, the diagnosis of kidney disease often surprises patients and may lead to denial, especially given that pain in the region of the kidneys and decrease in urinary volume are not clinical features. Par ticular aspects of the history that are germane to renal disease include a history of hypertension (which can cause CKD or more commonly be a consequence of CKD), diabetes mellitus, abnormal urinalyses, and preeclampsia or early pregnancy loss. A careful drug history should be elicited. Drugs to consider include nonsteroidal anti-inflammatory agents, cyclooxygenase-2 (COX2) inhibitors, antimicrobials, che motherapeutic agents, antiretroviral agents, proton pump inhibitors, phosphate-containing bowel cathartics, and lithium. In evaluating the uremic syndrome, questions about appetite, weight loss, nausea, hic cups, peripheral edema, muscle cramps, pruritus, and restless legs are especially helpful. A family history of kidney disease, together with assessment of manifestations in other organ systems such as auditory, visual, and integumentary, may lead to the diagnosis of a heritable form of CKD (e.g., Alport's or Fabry's disease, cystinosis) or shared environ mental exposure to nephrotoxic agents (e.g., heavy metals, aristolochic acid). It should be noted that clustering of CKD, sometimes of different etiologies, is often observed within families. The physical examination should focus on blood pressure and target organ damage from hypertension. Fundoscopy is especially important in the diabetic patient, because it may show evidence of diabetic reti nopathy, which is associated with diabetic nephropathy. Other mani festations of CKD include edema and sensory polyneuropathy. The finding of asterixis or a pericardial friction rub not attributable to other causes signifies the presence of the uremic syndrome. Laboratory Investigation Laboratory studies should focus on a search for clues to an underlying causative or aggravating disease pro cess and on the degree of renal damage and its consequences. Serum and urine protein electrophoresis, looking for multiple myeloma, should be obtained in all patients >35 years old with unexplained CKD, especially if there is associated anemia and elevated, or even

inappropriately normal, serum calcium concentration in the face of renal insufficiency. In the presence of hematuria or proteinuria, auto immune diseases such as lupus and underlying infectious etiologies such as hepatitis B and C and HIV should be tested. Serial measure ments of renal function should be obtained to determine the pace of deterioration and ensure that the disease is truly chronic, rather than acute or subacute and hence potentially reversible. Serum concentra tions of calcium, phosphorus, and PTH should be measured to evaluate metabolic bone disease. Hemoglobin concentration, iron, vitamin B12, and folate should also be evaluated. A 24-h urine collection may be helpful, because protein excretion >300 mg may be an indication for therapy with ACE inhibitors, ARBs, and SGLT2 inhibitors and also is associated with a higher risk of progression. If the patient has diffi culty in carrying out a 24-h urine collection, a random urine albumin/ creatinine or protein/creatinine is less accurate than a well-done 24-h collection but less cumbersome. Imaging Studies The most useful imaging study is a renal ultra sound, which can verify the presence of two kidneys, determine if they are symmetric, provide an estimate of kidney size, and rule out renal masses and evidence of obstruction. Because it takes time for kidneys to shrink as a result of chronic disease, the finding of bilaterally small kidneys supports the diagnosis of CKD of long-standing duration. If the kidney size is normal, it is possible that the kidney disease is acute or subacute. The exceptions are diabetic nephropathy (where kidney size is increased at the onset of diabetic nephropathy before CKD supervenes), amyloidosis, and HIV nephropathy, where kidney size may be normal in the face of CKD. Polycystic kidney disease that has reached some degree of renal failure will almost always present with enlarged kidneys with multiple cysts (Chap. 327). A discrepancy >1 cm in kidney length suggests either a unilateral developmental abnormality or a disease process or renovascular disease with arterial insufficiency affecting one kidney more than the other. The diagnosis of renovas cular disease can be undertaken with different techniques, including Doppler sonography, nuclear medicine studies, or CT or magnetic resonance imaging (MRI) studies. If there is a suspicion of reflux nephropathy (recurrent childhood urinary tract infection, asymmetric renal size with scars on the renal poles), a voiding cystogram may be indicated. However, in most cases, by the time the patient has CKD, the reflux has resolved, and even if still present, repair does not improve renal function. Radiographic contrast imaging studies are not particu larly helpful in the investigation of CKD. Intravenous or intraarterial dye should be avoided where possible in the CKD patient, especially with diabetic nephropathy, because of the risk of radiographic contrast dye–induced renal failure. When unavoidable, appropriate precaution ary measures include avoidance of hypovolemia at the time of contrast exposure, minimization of the dye load, and choice of radiographic contrast preparations with the least nephrotoxic potential. Additional measures thought to attenuate contrast-induced worsening of renal function include judicious administration of sodium bicarbonate–con taining solutions and N-acetylcysteine, although these agents may not be as effective as previously thought. Kidney Biopsy In the patient with bilaterally small kidneys, renal biopsy is not advised because (1) it is technically difficult and has a greater likelihood of causing bleeding and other adverse con sequences, (2) there is usually so much scarring that the underlying disease may not be apparent, and (3) the window of opportunity to render disease-specific therapy has passed. Other contraindications to renal biopsy include uncontrolled hypertension, active urinary tract infection, bleeding diathesis (including ongoing anticoagulation), and severe obesity. Ultrasound-guided percutaneous biopsy is the favored approach, but a surgical or laparoscopic approach can be considered, especially in the patient with a single kidney where direct visualization and control of bleeding are crucial. In the CKD patient in whom a kidney biopsy is indicated (e.g., suspicion of a concomitant or super imposed active process or in the face of accelerated loss of GFR), the bleeding time should be measured, and if increased, desmopressin should be administered immediately prior to the procedure.

A brief run of hemodialysis (without heparin) may also be consid ered prior to renal biopsy to normalize the bleeding time.

■ ■ESTABLISHING THE DIAGNOSIS AND ETIOLOGY OF CKD The most important initial diagnostic step is to distinguish newly diagnosed CKD from acute or subacute renal failure, because the latter two conditions may respond to targeted therapy. Previous measure ments of serum creatinine concentration are particularly helpful in this regard. Normal values from recent months or even years suggest that the current extent of renal dysfunction could be more acute, and hence reversible, than might otherwise be appreciated. In contrast, elevated serum creatinine concentration in the past suggests that the renal disease represents a chronic process. Even if there is evidence of chronicity, there is the possibility of a superimposed acute process (e.g., ECFV depletion, urinary infection or obstruction, or nephrotoxin exposure) supervening on the chronic condition. If the history suggests multiple systemic manifestations of recent onset (e.g., fever, polyar thritis, rash), it should be assumed that renal insufficiency is part of an acute systemic illness. Although kidney biopsy can usually be performed in early CKD (stages 1–3), it is not always indicated. For example, in a patient with a history of type 1 diabetes mellitus for 15–20 years with retinopathy, nephrotic-range proteinuria, and absence of hematuria, the diagno sis of diabetic nephropathy is very likely and biopsy is usually not necessary. However, if there is another finding not typical of diabetic nephropathy, such as hematuria or white blood cell casts, or absence of diabetic retinopathy, some other disease may be present and a biopsy may be indicated. CHAPTER 322 Chronic Kidney Disease In the absence of a clinical diagnosis, kidney biopsy may be the only recourse to establish an etiology in early-stage CKD. However, as noted above, once the CKD is advanced and the kidneys are small and scarred, there is little utility and significant risk in attempting to arrive at a specific diagnosis. Genetic testing is increasingly entering the repertoire of diagnostic tests since the patterns of injury and kidney morphologic abnormalities often reflect overlapping causal mechanisms, whose origins can some times be attributed to a genetic predisposition or cause (Table 322-2). The increased application of genetic testing has often yielded surprising diagnoses that deviate from the cause of CKD suggested by clinical or even kidney pathology alone. Given this realization and the cumulative significant contribution of monogenic disease etiologies, consideration is now given to large CKD gene panels, chromosomal microarrays, whole exome or even whole genome sequencing, and other advanced genetic analysis technologies in the evaluation and management of CKD. Suggested indications for such genetic evaluation in patients without a clinically evident etiology and course include family history (family member[s] with unexplained kidney failure, dialysis, or kidney transplant recipient; family member affected with maturity-onset dia betes of the young, kidney disease together with psychiatric morbidity, hearing or vision loss, autism spectrum disorder, developmental delay, and/or intellectual disability; multiple family members affected with similar phenotype); parental consanguinity; extrarenal involvement (dysmorphic facial features, autism spectrum disorder, developmental delay, and/or intellectual disability); multiple congenital structural kidney anomalies; steroid-resistant nephrotic syndrome; persistent active clinical or laboratory manifestations of glomerulonephritis or glomerular endotheliopathy; imaging consistent with cystic kidney dis eases/ciliopathies; young adult onset of unexplained progressive CKD; consideration of APOL1-mediated kidney disease; and unexplained kidney failure prior to kidney transplantation. TREATMENT Chronic Kidney Disease Therapy for CKD can be divided into interventions that are directed at the specific etiology and those that attenuate progression related to the common pathway of glomerular hyperfiltration, which

perpetuates kidney injury following reduced nephron mass, as discussed below. Treatments aimed at causes of CKD related to systemic diseases are discussed in the respective chapters. Recent developments in the etiology-directed therapy of CKD include the emergence of genome-specific therapies for certain patients with ADPKD (Chap. 327), siRNA therapy (lumasiran) for type 1 hyperoxaluria, and highly specific inhibitors for APOL1-mediated kidney disease (AMKD). Inaxaplin, a specific inhibitor of APOL1 channel function, has been shown to decrease urine protein excre tion in patients with focal segmental glomerulosclerosis caused by the high-risk genotypes at the APOL1 gene. In the absence of validated and specific biomarkers of imminent or ongoing kidney injury, the optimal timing for such specific therapies is usually well before there has been a measurable decline in GFR and certainly before CKD is established. It is helpful to measure sequentially and plot the rate of decline of GFR in all patients. Any acceleration in the rate of decline should prompt a search for superimposed acute or subacute processes that may be reversible. These include ECFV depletion, uncontrolled hypertension, urinary tract infection, new obstructive uropathy, exposure to nephrotoxic agents (e.g., nonsteroidal antiinflammatory drugs [NSAIDs] or radiographic dye), and reactiva tion or flare of the original disease, such as lupus or vasculitis. SLOWING THE PROGRESSION OF CKD There is variation in the rate of decline of GFR among patients with CKD. However, the several established and newer available interventions should be strongly considered in an effort to stabilize or slow the decline of renal function in most patients with reduced nephron mass at risk for progression from increased intraglomeru lar pressure and hyperfiltration as described above. Fortunately, these very same interventions also reduce cardiovascular compli cations of CKD and are therefore expected to greatly alleviate the global burden of CKD in the coming years to decades.

PART 9 Disorders of the Kidney and Urinary Tract Reducing Intraglomerular Hypertension and Proteinuria Increased intraglomerular filtration pressures and glomerular hypertrophy develop as a response to loss of nephron number. This response is maladaptive as it promotes the ongoing decline of kidney func tion even if the inciting process has been treated or spontaneously resolved. Control of glomerular hypertension is important in slow ing the progression of CKD. Moreover, elevated blood pressure increases proteinuria by increasing its flux across the glomerular capillaries. Conversely, the renoprotective effect of antihypertensive medications is gauged through the consequent reduction of pro teinuria. Thus, the more effective a given treatment is in lowering Normal TGF Impaired TGF Restored TGF Appropriate afferent arteriole tone Macula densa Afferent arteriole vasodilation

Normal GFR Increased Na+/glucose reabsorption Na+/glucose reabsorption SGLT-2 SGLT-2 SGLT-2 inhibition in proximal tubule Normal physiology Hyperfiltration in early stages of diabetic nephropathy SGLT-2 inhibition reduces hyperfiltration via TGF A B FIGURE 322-5 The postulated role of the gliflozins in generating tubuloglomerular feedback (TGF) to reduce intraglomerular hypertension. (Reproduced with permission from DZ Cherney et al: Cherney et al: Circulation 129:587, 2014.)

protein excretion, the greater is the subsequent impact on protec tion from decline in GFR. This observation is the basis for the treatment guideline establishing 130/80 mmHg as a target blood pressure in proteinuric CKD patients. Several controlled studies have shown that ACE inhibitors and ARBs are effective in slowing the progression of renal failure in patients with advanced stages of both diabetic and nondiabetic CKD, in large part through effects on efferent vasodilatation and the subsequent decline in glomerular hypertension. The combina tion of these two classes should be avoided, due to a demonstrated greater incidence of AKI and adverse cardiac events from such combination therapy. While a nonprogressive decrease in eGFR of up to 30% may be a tolerable reflection of effective unloading of glomerular hyperfiltration, a progressive increase in serum creati nine concentration with these agents may suggest the presence of renovascular disease within the large or small arteries. Together with efferent arteriolar vasodilation, afferent vasocon striction should reduce intraglomerular pressure. Indeed, gliflozins, which are a family of inhibitors of SGLT2 transporters in the proxi mal tubule, result in precisely this glomerular response by activat ing tubuloglomerular feedback (Fig. 322-5) and are indicated in slowing the decline of GFR in both diabetic and nondiabetic kidney disease. Other more direct cellular protective mechanisms of the gliflozins have been invoked in kidney and other tissues. This class of agents also has been demonstrated to reduce major cardiovascu lar events in CKD patients. Recent studies have also shown that the glucagon-like peptide receptor agonists reduce major cardiovascu lar events and

CKD in at-risk patients. Among the calcium channel blockers, diltiazem and verapamil may exhibit superior antiproteinuric and renoprotective effects com pared to the dihydropyridines. At least two different categories of response can be considered: one in which progression is strongly associated with systemic and intraglomerular hypertension and pro teinuria (e.g., diabetic nephropathy, glomerular diseases) and in which ACE inhibitors and ARBs are recommended choices, and another in which proteinuria is mild or absent initially (e.g., ADPKD and other tubulointerstitial diseases), where the contribution of intraglomerular hypertension is less prominent and other antihy pertensive agents can be useful for control of systemic hypertension. MANAGING OTHER COMPLICATIONS OF CKD Medication Dose Adjustment Although the loading dose of most drugs is not affected by CKD because renal elimination is not used in the calculation, the maintenance doses of many drugs will need to

Normalization of GFR Decreased Na+ delivery to macula densa Elevated GFR Increased Na+ delivery to macula densa Afferent arteriole constriction

Na+

Glucosuria C

be adjusted. For those agents in which >70% excretion is by a non renal route, such as hepatic elimination, dose adjustment may not be needed. Some drugs that should be avoided include metformin, meperidine, and oral antihyperglycemics that are eliminated by the kidney. NSAIDs including COX2 inhibitors should be avoided because of the risk of further worsening of kidney function. Many antibiotics, antihypertensives, and antiarrhythmics may require a reduction in dosage or change in the dose interval. Several online Web-based databases for dose adjustment of medications according to stage of CKD or estimated GFR are available (e.g., http://www. globalrph.com/index_renal.htm). Nephrotoxic radiocontrast agents and gadolinium should be used according to strict guidelines when medically necessary, as discussed above. PREPARATION FOR RENAL REPLACEMENT THERAPY (See also Chap. 325.) Temporary relief of symptoms and signs of impending uremia, such as anorexia, nausea, vomiting, lassitude, and pruritus, may sometimes be achieved with dietary protein restriction. However, this diet carries a risk of malnutrition; thus, plans for more long-term management should be in place. Maintenance dialysis and kidney transplantation have extended the lives of hundreds of thousands of patients with CKD world wide. Clear indications for initiation of renal replacement therapy for patients with CKD include anorexia and nausea not attribut able to reversible causes such as peptic ulcer disease, evidence of malnutrition, and fluid and electrolyte abnormalities, principally hyperkalemia or ECFV overload, that are refractory to other mea sures. Encephalopathy and pericarditis are very late complications, so it is now rare that they serve as indications for initiation of renal replacement therapy. Recommendations for the Optimal Time for Initiation of Renal Replacement Therapy Because of the individual variability in the severity of uremic symptoms and renal function, it is ill-advised to assign an arbitrary urea nitrogen or creatinine level to the need to start dialysis. Moreover, patients may become accustomed to chronic uremia and deny symptoms, only to find that they feel better with dialysis and realize in retrospect how poorly they were feeling before its initiation. Previous studies suggested that starting dialysis before the onset of severe symptoms and signs of uremia was associated with pro longation of survival. This led to the concept of “healthy” start and is congruent with the philosophy that it is better to keep patients feeling well rather than allowing them to become ill with uremia and then attempting to return them to better health with dialysis or transplantation. Although recent studies have not confirmed an association of early-start dialysis with improved patient survival, there may be merit in this approach for some patients. At a practi cal level, advanced preparation may help to avoid problems with the dialysis process itself (e.g., a poorly functioning fistula for hemo dialysis or malfunctioning peritoneal dialysis catheter) and, thus, preempt the morbidity associated with resorting to the insertion of temporary hemodialysis access with its attendant risks of sepsis, bleeding, thrombosis, and association with accelerated mortality. Patient Education Social, psychological, and physical preparation for the transition to renal replacement therapy and the choice of the optimal initial modality are best accomplished with a gradual approach involving a multidisciplinary team. Along with conserva tive measures discussed in the sections above, it is important to prepare patients with an intensive educational program, explain ing the likelihood and timing of initiation of renal replacement therapy and the various forms of therapy available and the option of nondialytic conservative care. The more knowledgeable that patients are about hemodialysis (both in-center and home-based), peritoneal dialysis, and kidney transplantation, the easier and more appropriate will be their decisions. Patients who are provided with education are more likely to choose home-based dialysis therapy. This approach is of societal benefit because home-based therapy is less expensive in most jurisdictions and is associated with improved

quality of life. The educational programs should be commenced no later than stage 4 CKD so that the patient has sufficient time and cognitive function to learn the important concepts, make informed choices, and implement preparatory measures for renal replace ment therapy.

Exploration of social support is also important. Early education of family members for selection and preparation of a home dialy sis helper or a biologically or emotionally related potential living kidney donor should occur long before the onset of symptomatic renal failure. Kidney transplantation (Chap. 325) offers the best potential for complete rehabilitation because dialysis replaces only a small fraction of the kidneys' filtration function and none of the other renal functions, including endocrine and anti-inflammatory effects. Generally, kidney transplantation follows a period of dialysis treat ment, although preemptive kidney transplantation (usually from a living donor) can be carried out if it is certain that the renal failure is irreversible and, under such circumstances, is preferred to trans planting after a period of dialysis. ■ ■IMPLICATIONS FOR GLOBAL HEALTH In contrast to the natural decline and successful eradication of many devastating infectious diseases, there is rapid growth in the prevalence of metabolic and vascular disease in developing countries. Diabetes mellitus is becoming increasingly prevalent in these countries, perhaps due in part to change in dietary habits, diminished physical activity, and weight gain. Therefore, it follows that there will be a proportionate increase in vascular and renal disease. According to a recent analysis, in the absence of effective implementation of significant preventive and therapeutic inroads, a forecasting analysis for the U.S. popula tion suggests that the number of global years of life lost (YLLs) due to CKD is expected to rise from a prior value of ~26 million in 2016 to 52.5 million in 2040, accompanied by a rise in mortality from 1.2 million in 2016 to 3.1 million in 2040. These increases are predicted to move CKD in the YLL rankings from 16th in 2016 to 5th in 2040. This rise will be disproportionately large in many other regions of the world where CKD prevalence is already rising at alarming rates due to population aging and the rapid increase in diabetes, hypertension, and obesity. CHAPTER 322 Chronic Kidney Disease Health care agencies must plan for improved screening of high-risk individuals for early detection, prevention, and treatment plans in these nations and must start considering options for improved avail ability of renal replacement therapies. There is also increasing recognition of endemic nephropathies in developing countries that particularly target young males working in agriculture. The extent of morbidity and mortality associated with these nephropathies is only starting to be appreciated. It is unclear what the cause is, but population genetic risk, endemic nephrotoxins, expo sure to pesticides, NSAID use, and chronic volume depletion have all been suggested to contribute. Global warming and air pollution have also been implicated in the development of kidney diseases. ■ ■FURTHER READING Bhandari S et al: Renin-angiotensin system inhibition in advanced chronic kidney disease. N Engl J Med 387:2021, 2022. Chertow G et al: Effects of dapagliflozin in stage 4 chronic kidney disease. J Am Soc Nephrol 32:2352, 2021. Dahl NK et al: The clinical utility of genetic testing in the diagnosis and management of adults with chronic kidney disease. J Am Soc Nephrol 34:2039, 2023. Egbuna OL et al: Inaxaplin for proteinruic kidney disease in persons with two APOL1 variants. N Engl J Med 388:969, 2023. Kovesdy CP: Epidemiology of chronic kidney disease: An update 2022. Kidney Int Suppl (2011) 12:7, 2021. Vivante A: Genetics of chronic kidney disease. N Engl J Med 391:627, 2024. Yu JH et al: GLP-1 receptor agonists in diabetic kidney disease: Current evidence and future directions. Kidney Res Clin Pract 41:136, 2022.

Revision #1
Created 2026-01-06 16:34:21 UTC by Omar Ayman
Updated 2026-01-06 16:34:21 UTC by Omar Ayman