# Renal Disease and Failure

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### *Faculty Disclosure*

Contributing faculty, Carol Whelan, APRN, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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The division planner and director have disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

### *Audience*

This course is designed for nurses involved in the care of patients with kidney disease or failure.

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### Course Objective

The purpose of this course is to provide primary care clinicians with the information necessary to appropriately identify and treat renal disease, with the objective of minimizing the long-term effects and complications of the disease.

### Learning Objectives

*Upon completion of this course, you should be able to:*

1. Define the various types of renal failure and disease.
2. Describe the impact of renal disease on public health.
3. Outline the pathophysiology of chronic kidney disease and renal failure.
4. Identify the clinical signs and symptoms of chronic kidney disease and renal failure.
5. Discuss the diagnostic tests used to identify and stage renal failure.
6. Analyze the management of the various stages of renal failure, including potential cardiovascular, hematologic, metabolic, and psychologic complications.
7. Compare and contrast various aspects of hemodialysis and peritoneal dialysis.
8. Discuss the process and indications for renal transplantation.
9. Evaluate the risks of using contrast media in patients with existing renal disease.
10. Identify special considerations for renal disease in specific patient populations.
11. Analyze possible mental health issues that may arise in patients with renal disease.
12. Describe the key aspect of patient and family teaching for each stage of renal failure.


Sections marked with this symbol include evidence-based practice recommendations. The level of evidence and/or strength of recommendation, as provided by the evidence-based source, are also included so you may determine the validity or relevance of the information. These sections may be used in conjunction with the course material for better application to your daily practice.

## INTRODUCTION

Renal failure is a complex and challenging health issue that demands the involvement of specialists, primary care providers, and nurses. Patient education in renal failure requires careful coordination and a complete knowledge of the conditions and precipitating factors. By gradually introducing different educational materials and enabling the patient to help control the course of the disease, the healthcare provider can help restore a sense of independence and confidence in the patient. This course will outline the causes and contributing factors associated with various forms of renal disease. The key aspects of diagnosis, including differential diagnosis, will be thoroughly discussed. Finally, the components of the dialysis and non-dialysis management of patients with renal disease, including the need for referral and in-depth patient education, will be provided.

## AN OVERVIEW OF RENAL DISEASE

### DEFINITIONS

Renal disease is a serious health issue, affecting an ever-increasing number of patients and resulting in substantial financial costs in the United States. The total investment in kidney-related research across the entire National Institutes of Health is estimated to be $704 million in 2024 [1]. In 2021, the Medicare program spent $67,993 per person per year for the care of patients with end-stage kidney failure [2]. Renal disease demands the involvement of many other healthcare personnel, including mental health professionals. Renal disease generally falls into one of two categories: chronic kidney disease (CKD) or acute kidney injury (AKI) [3; 4].

CKD is defined as a reduction in kidney function or kidney damage that has been present for at least three months [3; 4; 5; 6]. However, CKD should not be viewed in simple mathematic terms. It is an ongoing process of renal injury that causes compensatory hyperfiltration in less-affected glomeruli, which eventually leads to the destruction of those glomeruli as well [3]. Left untreated, this ongoing destruction results in a steady decline in renal function, which eventually affects not just the renal system but almost every organ system in the body [3; 4].

AKI is defined as an increase in serum creatinine of 0.3 mg/dL or more within 48 hours; or an increase in serum creatinine of more than 1.5 times the baseline within the prior 7 days; or urine volume less than 0.5 mL/kg/hour for 6 hours. AKI may be classified either by the physiologic cause (i.e., prerenal, intrarenal, or postrenal) or by the amount of urine produced (i.e., anuric, oliguric, or nonoliguric) [7; 8].

The term end-stage renal disease (ESRD) refers to disease that requires either dialysis or transplantation services. In the United States, 98% of all patients receiving dialysis or transplantation have a glomerular filtration rate (GFR) <15 mL/min/1.73 $m^2$ [9]. Therefore, the terms ESRD and kidney failure are often used interchangeably. Although ESRD is generally associated with a GFR less than 15 mL/min/1.73 $m^2$, it is more importantly an administrative term, as patients receiving dialysis or transplantation services are covered by the Medicare ESRD program [10]. In some cases, ESRD is also used rather loosely to refer to patients who are experiencing progressive CKD and are expected to begin dialysis in a matter of days or weeks.

Practice guidelines published by the National Kidney Foundation (NKF) and the Kidney Disease: Improving Global Outcomes (KDIGO) Network define and classify CKD based on GFR category [6; 9]. KDIGO guidelines also include the identification of cause and albuminuria category in its classification system [6]. These staging systems are used to predict CKD progression and associated complications (***Table 1***), with an emphasis on predicting the development of cardiovascular disease, the leading cause of death in patients with ESRD and the cause of dramatically increased mortality rates in patients with even moderate kidney disease. Identifying and staging patients with impaired renal function is important in order to prevent or slow the onset of CKD and its complications.

| CLASSIFICATION OF CHRONIC KIDNEY DISEASE | | | |
|---|---|---|---|
| **GFR Status** | | | |
| **Category** | **Description** | | |
| 1 | Kidney damage with normal or elevated GFR (≥90 mL/min/1.73 $m^2$) | | |
| 2 | Kidney damage with mild decrease in GFR (60–89 mL/min/1.73 $m^2$) | | |
| 3a | Mild-to-moderate decrease in GFR (45–59 mL/min/1.73 $m^2$) | | |
| 3b | Moderate to severe decrease in GFR (30–44 mL/min/1.73 $m^2$) | | |
| 4 | Severe decrease in GFR (15–29 mL/min/1.73 $m^2$) | | |
| 5 | Kidney failure (<15 mL/min/1.73 $m^2$ or requires dialysis) | | |
| **Albuminuria Status** | | | |
| **Category** | **AER** | **ACR** | **Description** |
| A1 | <30 mg/24 hrs | <30 mg/g | Normal to mild increase |
| A2 | 30–300 mg/24 hrs | 30–300 mg/g | Moderate increase |
| A3 | >300 mg/24 hrs | >300 mg/g | Severe increase |
| AER = albumin excretion rate; ACR = albumin-to-creatinine ratio. | | | |
| *Source: [6; 9]* | | | *Table 1* |

A common marker of CKD is proteinuria, which is first detectable as microalbuminuria (i.e., >30 mg albumin in a 24-hour urine collection). Due to the difficulty of measuring 24-hour urine protein excretion, proteinuria is usually screened using dipstick or a spot urine albumin-creatinine ratio. Other indicators include abnormal urine sediment or abnormal imaging studies.

GFR is the best measure of kidney function. Normal adult GFR is 120–130 mL/min/1.73 $m^2$, but it declines naturally with age. Definitions of CKD are not age-adjusted, and therefore the prevalence of CKD increases with age.

True determination of GFR is made by collecting urine for 24 hours in tandem with a serum creatinine measurement. Patient compliance with urine collection can prove quite difficult and 24 hours may be too long to wait, so many clinicians rely on indirect calculators such as the estimated GFR (eGFR), which determines GFR based on numerous biomarkers including serum creatinine [6].

## EPIDEMIOLOGY

Although exact statistics regarding the prevalence of mild-to-moderate renal failure are not available, the epidemiology of ESRD has been widely documented by the U.S. Renal Data System (USRDS), which collects statistics on all Medicare patients on dialysis. Since 1974, Medicare coverage has been extended to virtually all patients on dialysis in the United States; therefore, these data are highly representative of the current dialysis population. According to the USRDS, the number of patients with ESRD in the United States was 807,337 in 2019, an increase of 88.2% since 2002 [11]. Among patients with incident ESRD in 2021, 7.9% were waitlisted prior to ESRD onset or received a kidney transplant as their initial ESRD treatment modality. Although this percentage was relatively low, it represents an increase from 6.4% in 2011 [11].

The two leading causes of ESRD are diabetes (38% of new patients) and hypertension (27% of new cases) [12]. New cases of ESRD with diabetes or hypertension listed as the primary cause had been rising rapidly since 1980, but each has declined from 2000 to 2016 [13; 14]. Other less common causes of ESRD include glomerulonephritis, interstitial nephritis, autosomal dominant polycystic kidney disease (the leading genetic cause), and collagen vascular disease. Due to the prevalence of kidney transplantation, post-transplantation kidney disease has become the fourth largest cause of ESRD in the United States; however, these patients are reported within their original disease category for epidemiologic purposes [15]. New cases of diabetic ESRD are expectedly higher with increasing age in all racial groups, but generally lower among younger individuals [11]. Statistically, non-whites are four times more likely to require dialysis. Adjusted ESRD prevalence increases with advancing age, with 7,048 cases per million people 65 to 74 years of age and 7,380cases per million people 75 years of age and older. Adjusted ESRD prevalence in Black, White, and Asian individuals was essentially unchanged between 2021 and 2022. However, adjusted ESRD prevalence in Black Americans was 23 times higher than in White Americans in 2022; 14 years earlier, that ratio was 3.8, highlighting the slow progress in addressing the disparity in ESRD prevalence [11].

AKI is primarily a disease of hospitalized patients and often is the result of pre-existing chronic kidney disease [11]. The adjusted rate of first hospitalization with AKI during a year among Medicare fee-for-service beneficiaries increased by approximately 32% over 10 years, from 32.5 admissions per 1,000 person-years in 2012 to 42.7 admissions per 1,000 person-years in 2022 [11]. AKI rates are significantly associated with aging and with white race [11]. The most common causes of AKI vary according to pathophysiology, but possible etiologies include trauma, dehydration/volume depletion, tubulointerstitial disease, glomerulonephritis, and obstruction [3; 8].

### PATHOPHYSIOLOGY OF KIDNEY DISEASE

The basic pathophysiology of CKD is that of renal injury and loss of functioning nephrons, the mechanism of which depends on the underlying cause. The result is hyperfiltration in the surviving glomeruli (in an attempt by the body to increase GFR), which then causes ongoing glomerular stress, renal injury, and eventually glomerular destruction [3; 5]. This leads to a decrease in GFR and a continuance of the hyperperfusion destruction syndrome. Allowed to continue, the patient will inevitably develop ESRD and require dialysis or transplantation to avoid death from uremia. When treatment to reverse this process is initiated prior to the patient losing more than 40% to 50% of renal function, stabilization is possible. After a patient has lost more than 50% to 60% of renal function, failure is considered inevitable.

The pathophysiology of AKI depends on the site of occurrence. Prerenal AKI, the most common type, is caused by renal hypoperfusion (most likely from dehydration) [16]. Intrarenal or intrinsic AKI, the result of damage to the renal parenchyma, may be a result of prolonged prerenal AKI (leading to acute tubular necrosis), toxins, interstitial disease, vascular disease, or acute glomerular disease [16]. Postrenal (obstructive) AKI results from physical obstruction of urine outflow and may be caused by neoplasm, prostatic enlargement, bladder dysfunction, or nephrolithiasis [3; 16; 17].

## CLINICAL PRESENTATION

### CKD

The clinical presentation of CKD is often subtle, and symptoms are uncommon with a GFR greater than about 35 mL/min/1.73 $m^2$. Therefore, suspicion for mild renal disease should be based on recognition of the primary pathologic mechanism responsible for renal injury, particularly in patients with diabetes and/or hypertension. It is equally important to begin early screening for the complications of renal disease to prevent morbidity and to establish a credible baseline for the individual patient.

After the GFR falls to less than 35 mL/min/1.73 $m^2$, a variety of metabolic, psychiatric, hematologic, cardiovascular, and acid-base regulatory problems occur (***Table 2***). Clinical presentation at this point depends on the particular complication and the underlying cause of renal failure [3; 4; 5; 17; 18].

### AKI

The usual clinical presentation of AKI includes signs and symptoms of accumulation of nitrogen in the blood, such as fatigue, headache, anorexia, nausea, and vomiting. Potassium imbalances can result in tachycardia. Patients at highest risk for prerenal AKI have pre-existing CKD, have recently undergone surgery, been exposed to radiocontrast dye, have received aminoglycoside antibiotics, or have developed sepsis [8]. Postrenal AKI is associated with flank or abdominal pain and possibly neurologic symptoms. Most patients with AKI have identifiable risk factors, such as CKD, advanced age, liver disease, diabetes, or vascular disease [8]. Therefore, it is possible and essential to identify those at high risk before AKI develops in order to minimize damage.

| MAJOR COMPLICATIONS OF CHRONIC RENAL FAILURE |
|---|
| **Cardiovascular Complications** |
| Atherosclerosis |
| Congestive heart failure |
| Hypertension |
| Pulmonary edema |
| Pericarditis |
| **Metabolic Complications** |
| Hyperkalemia |
| Metabolic acidosis |
| Alterations in vitamin D, calcium, and phosphorus metabolism and absorption |
| Hyperparathyroidism |
| Renal osteodystrophies |
| Hyperlipidemia |
| Nausea, vomiting |
| Anorexia |
| **Psychosocial Complications** |
| Depression/suicide |
| Insomnia |
| Sexual dysfunction |
| Impoverishment |
| Unemployment |
| **Hematologic Complications** |
| Anemia |
| Leukopenia |
| Erythropoietin deficiency |
| *Source: Compiled by Author* — *Table 2* |

## DIAGNOSIS

### PHYSICAL EXAMINATION

The physical examination of patients with suspected renal disease or failure should include both a focused examination to identify pathologic processes caused by the primary disease entity (e.g., diabetes or hypertension) and a broader examination to identify the effects of progressive renal failure. Areas of importance include assessment of vital signs (including measurement of bilateral and orthostatic blood pressure); funduscopic evaluation for signs of arteriovenous (AV) nicking, diabetic retinopathy, and papilledema; assessment of volume status by determination of jugular vein distention; auscultation of lung sounds; assessment for edema or ascites; and assessment of heart sounds to screen for volume overload and pericarditis. A full abdominal examination is also recommended and should include auscultation for renal artery bruits; examination of the skin for ecchymosis, rashes (especially those suggesting collagen vascular disorders), or uremic frost (although this would indicate extremely advanced disease); percussion of the bladder to exclude distention; rectal examination; and evaluation of the prostate in male patients to exclude obstruction [17]. Formal and informal mental status examinations should be included to screen for depression, confusion, delirium, and other psychiatric complications.

| PROTEIN EXCRETION VALUES | |
|---|---|
| **Category** | **Value** |
| **Total Protein Excretion** | |
| Normal | <150 mg/day |
| Proteinuria | ≥150 mg/day |
| Nephrotic-range proteinuria | >3,500 mg/day |
| **Albumin Excretion** | |
| Normal | 2–30 mg/day |
| Microalbuminuria | 30–300 mg/day |
| Macroalbuminuria | >300 mg/day |

*Source: Kashif W, Siddiqi N, Dincer AP, Dincer HE, Hirsch S. Proteinuria: how to evaluate an important finding. Cleve Clin J Med. 2003;70(6):535-547. Reprinted with permission. Copyright © 2003 Cleveland Clinic Foundation. All rights reserved.* *Table 3*

## LABORATORY TESTS

The most important tool in monitoring patients with suspected and diagnosed renal failure or those at risk for developing renal disease is dipstick urinalysis, which should be performed at virtually every office visit. Urine dipstick testing is highly specific (although false positives do occur) but less sensitive than quantitative testing. The presence of proteinuria should alert the clinician to perform a full 24-hour urine analysis for protein and creatinine clearance (***Table 3***). All patients with diabetes who are negative for macroscopic proteinuria on dipstick testing should have laboratory testing for microalbuminuria, as early identification and treatment can improve prognosis. This testing should be initiated at the time of diagnosis for patients with type 2 diabetes and within two years of diagnosis for patients with type 1 diabetes [19].

The importance of dipstick testing in high-risk individuals, especially African Americans, diabetics, and hypertensives, cannot be overstated. Many institutions rely on serum creatinine measurements to identify renal disease. However, serum creatinine is not sufficiently sensitive for renal disease, with levels failing to rise above normal until the patient's GFR is less than 60 mL/min/1.73 $m^2$ and the progression to ESRD has already become inevitable [20]. Other biomarkers have been identified, including serum cystatin C and creatinine clearance and may be used in addition to GFR to identify the presence of renal disease [6; 21]. Novel biomarkers specific to AKI may be useful, as these cases have generally been diagnosed using serum creatinine in the past due to the unreliability of GFR measurements [20; 22; 23; 24; 25]. Overall, early monitoring, early intervention, and tight control of modifiable risk factors could help many patients avoid the progression to ESRD.

After a patient has been diagnosed with renal disease, a baseline should be established by obtaining (in addition to the urinalysis) a full chemistry panel, including electrolytes, fasting blood glucose, magnesium, phosphorus, ionized calcium, total serum protein, serum albumin, blood urea nitrogen (BUN), creatinine, liver enzymes, lipid profile, complete blood count (CBC), and intact parathyroid hormone (iPTH) [21]. In addition, hepatitis B and C and HIV serology should be obtained [21].

## IMAGING STUDIES

In some patients, renal biopsy and nuclear imaging may be helpful [21]. However, the risks associated with invasive tests or exposure to contrast dye compels consultation with a nephrologist before subjecting the patient to potential complications.

Although imaging studies are not particularly useful in diagnosing the extent of renal disease, renal ultrasound is recommended to determine the presence of cysts or obstruction and to document the size of the kidneys [17; 18; 21]. This is necessary, as CKD characteristically results in smaller than average kidneys, whereas AKI is characterized by normal or even enlarged kidneys. Asymmetry may be a result of unilateral renal artery stenosis.

### DIFFERENTIAL DIAGNOSIS

The main issue in the diagnosis of CKD is exclusion of AKI. AKI is a potentially reversible, life-threatening condition, and all patients with AKI should be hospitalized. As noted, the most common type of AKI seen in primary care is prerenal AKI (caused by renal hypoperfusion) related to volume depletion or hypotension related to pre-existing risk factors, such as CKD, advanced age, liver disease, diabetes, or vascular disease [8]. Some patients with CKD have a small degree of reversible prerenal AKI caused by hypovolemia or alterations in renal hemodynamics that result in renal hypoperfusion (e.g., from nonsteroidal anti-inflammatory drugs [NSAIDs] or angiotensin-converting enzyme [ACE] inhibitors) [8].

Urinalysis is highly diagnostic in differentiating between AKI and CKD. Prerenal AKI is usually accompanied by urine osmolality of more than 500 mOsm/kg, specific gravity of more than 1.020, and hyaline casts. Intrarenal AKI results in a urine osmolality of approximately 300 mOsm/kg, with a specific gravity of around 1.010, tubular casts, tubular cells, and a distinctive brownish, muddy appearance of the urine due to brown granular casts [18; 26].

Occasionally, outpatients may be seen with postrenal obstructive AKI. A distended bladder, flank pain, and prostatic enlargement are potential signs. Ultrasound imaging virtually always detects obstruction in these patients [18].

If, after a thorough history and physical examination, AKI is still considered a potential diagnosis, the patient should be urgently referred to a renal specialist. Renal ultrasound evaluation or biopsy may be necessary for a definitive diagnosis.

Vigilance is necessary to determine any underlying correctable pathologic process that may be causing renal failure. Renal vascular hypertension should always be considered when renal function deteriorates rapidly with the initiation of ACE inhibitors or when abdominal bruits are heard on auscultation.

## MANAGEMENT OF CHRONIC RENAL DISEASE

An intensive and multifactorial management approach is required for patients with renal disease in order to address all risk determinants. The mainstays of treatment are lifestyle modification, management of complications and/or comorbidities, and dialysis for patients with severe or late-stage disease. Some patients may be candidates for kidney transplant, although the wait for a non-related donor can be long. Finally, psychosocial issues and patient education (primarily to ensure compliance with the established treatment plan) are important as well.

### STAGES 1 AND 2: MILD CHRONIC RENAL DISEASE

Almost all patients with stage 1 and stage 2 CKD are managed in primary care. Stage 1 CKD is kidney disease with normal kidney function. Kidney function in stage 2 is 60% to 90% [27]. The emphasis for these patients is identifying and managing risk factors, monitoring progression of renal impairment, and beginning patient education. It is important to remember that the risk of cardiovascular events is higher in patients with early CKD than advancement to dialysis or kidney transplantation [27]. Therefore, interventions to address cardiovascular risk factors are warranted, including increased physical activity, dietary changes, smoking cessation, and possibly pharmacologic treatment of hyperlipidemia or hypertension. Factors that indicate an increased risk of advancement to higher stages of kidney disease include [27]:

- Proteinuria (albumin-to-creatinine ratio >70 mg/mmol or protein-to-creatinine ratio >100 mg/mmol)

- Hematuria of renal origin
- Declining GFR (Loss of 5 mL/min/1.73 $m^2$ over one year or less or loss of 10 mL/min/1.73 $m^2$ over five years or less)
- Young age at diagnosis
- Family history of renal failure
- Hypertension that is difficult to control

**Monitoring and Testing**

As proteinuria and hematuria can be indicators of progressive disease, these levels should be assessed at diagnosis and annually thereafter [27]. Evidence of deteriorating renal function should initiate further evaluation or referral to a specialist.

All patients with stage 1 and stage 2 disease should have at least yearly evaluation of creatinine, urinary protein, and blood pressure levels. The maximum blood pressure target for these patients is <140/90 mm Hg; however, in the presence of higher urinary protein levels, the maximum target is <130/80 mm Hg [27].

Cardiovascular risk should also be assessed and addressed annually. Patients should be counseled regarding smoking, exercise, and lifestyle. Cholesterol-lowering therapy should be considered in patients with evidence of macrovascular disease or with an estimated 10-year risk of cardiovascular events ≥20% [27].

**Treatment for the Prevention of Disease Progression**

In 2021, the U.S. Food and Drug Administration (FDA) approved dapagliflozin to reduce the risk of kidney function decline, kidney failure, cardiovascular death, and hospitalization for heart failure in adults with CKD who are at risk of disease progression [28]. Dapagliflozin is a sodium glucose co-transporter 2 (SGLT2) inhibitor. By inhibiting SGLT2 in the proximal renal tubules, dapagliflozin reduces the reabsorption of filtered glucose from the tubular lumen and lowers the renal threshold for glucose [29]. Dapagliflozin also reduces sodium reabsorption and increases sodium delivery to the distal tubule, which may decrease cardiac preload/afterload, downregulate sympathetic activity, and decrease intraglomerular pressure [29]. The FDA's decision followed presentation of results from the Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) trial [30]. The trial randomly assigned 4,304 participants to receive dapagliflozin 10 mg once daily or placebo. The primary outcome was a composite of a sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes. Over a median of 2.4 years, a primary outcome event occurred in 197 of the 2,152 participants in the dapagliflozin group and in 312 of the 2,152 participants in the placebo group [30]. Dapagliflozin is not recommended for patients who are on dialysis treatment [28].

## STAGE 3: MODERATE CHRONIC RENAL DISEASE

**Monitoring and Testing**

As with stage 1 and stage 2 patients, most patients with stage 3 CKD can be appropriately managed in primary care. Again, the aim is to identify individuals at risk for progressive renal disease and to reduce associated risks [31]. Although stage 3 CKD produces relatively few symptoms, interventions to decrease morbidity and mortality and to slow or even halt the progression of renal failure are most effective at this stage. Therefore, the first goal in the management of patients with moderate CKD is accurate diagnosis and monitoring via screening tools such as urine dipstick testing for protein, measurement of urinary albumin excretion (rates greater than 30 mg/24 hours have been shown to be a precursor for diabetic nephropathy), and the measurement of urinary creatinine clearance [32]. A timed urine collection, generally a 24-hour collection, has been the longstanding "gold standard" for quantitative evaluation of proteinuria. However, the NKF and KDIGO guidelines recommend adopting the use of untimed or "spot" urine measurements that compare the concentration of protein to the concentration of creatinine [6; 9]. Evidence of benefit exists for lowering urinary protein excretion rates to less than 1 g/day; reduction of proteinuria is protective of both the renal and cardiovascular systems [6; 9].

ACE inhibitors and angiotensin receptor blockers (ARBs) should be used aggressively at moderate-to-high doses. It has been suggested that these drugs may be beneficial when used in combination; however, there is some concern regarding increased risk for adverse events with combination therapy [6; 9; 33]. Evidence of its efficacy is limited, and one major trial supporting this approach (the COOPERATE trial) has been retracted [34; 35]. If attempted, serum potassium levels must be monitored, and the use of a mild diuretic may help normalize levels. Even in the presence of mild renal disease, thiazide diuretics can cause severe hypokalemia, so use must always be monitored. ACE inhibitor and ARB therapy used concomitantly with the thiazide diuretic may result in a normal potassium level, but levels should always be checked if one of the drugs is stopped or dosage is altered.

Progression of CKD should be monitored regularly via creatinine clearance; providers should not rely solely on estimates of renal function based on serum creatinine. Urine should also be regularly examined by dipstick and microscopic analysis, with measurement of specific gravity, proteinuria, hematuria, pyuria, and sediment. Any urine sample should also be analyzed for total protein in addition to creatinine clearance. Specific patient instruction should accompany the order for spot urine collection.

For patients with diabetes, glycosylated hemoglobin (HbA1c) should be monitored. Levels of 7% or less are ideal; 6% or less is considered normal [6; 19]. However, studies of older patients who have concomitant coronary artery disease (CAD) suggest that very tight control (targeting to 6%) may lead to increased morbidity and mortality [36; 37].

It is well established that anemia develops in the course of CKD and is nearly universal in patients with kidney failure. Therefore, a full anemia work-up should be done for these patients. Measurement of hemoglobin, rather than hematocrit, is the preferred method for assessing anemia [9]. Unlike hematocrit, hemoglobin measurement gives an absolute value and is not affected greatly by shifts in plasma water (e.g., with use of diuretics or dialysis). Acceptable (normal) hemoglobin levels have not been defined for patients with kidney disease, and anemia is defined according to physiologic norms. Patients with hemoglobin levels lower than these norms are considered anemic [9]. Individual patients trend toward a fall in hemoglobin as kidney function declines. This is most likely the result of decreased production of erythropoietin. However, erythropoietin levels are not a useful measure of anemia in CKD because they often are not elevated, despite low hemoglobin levels [9].

The work-up should also include determining if the anemia is the result of iron deficiency, in which case the patient (especially men and non-menstruating women) should be referred to a gastroenterologist for further testing and treatment. Anemia with low reticulocyte counts or increased measure of destruction (non-iron deficiency) may be the result of myelodysplasia [9]. As noted, declining kidney function is associated with decreased production of erythropoietin, which can be identified by measurements of serum erythropoietin. Also, many drugs associated with the treatment of renal disease and hypertension (such as hydralazine or even rarely allopurinol) may cause anemia. If anemia develops as a result of CKD, referral to a nephrologist is warranted [9].

Primary care practitioners should also ensure that all disease-specific assessments are run based on the individual patient's pathology. For example, patients with diabetes will require regular measurement of lipids (with a low-density lipoprotein [LDL] goal of 70 mg/dL), HbA1c, CBC, thyroid-stimulating hormone (TSH), and complete metabolic panel as well as regular foot, eye, and skin exams. Patients with hypertension should have consistent testing of uric acid levels, CBC, metabolic panel, and lipids (again with an LDL goal of 70 mg/dL). The clinical decision as to how often these laboratory values should be monitored depends on the severity of the renal disease and the presence of abnormalities in previously recorded values.

**Cardiovascular Management and Complications**

While cardiovascular complications are recognized as the leading cause of death among patients with ESRD, accounting for more than 50% of deaths in the first year of dialysis, studies have shown that even mild-to-moderate renal disease (defined as an elevated serum creatinine between 1.2 mg/dL and 1.4 mg/dL) is an independent risk factor for cardiovascular events [5; 6; 38]. A meta-analysis of 38,000 patients revealed a 19% to 21% increase in the need for thrombolytic therapy in patients with a GFR less than 70 mL/min/1.73 $m^2$ compared to patients with normal GFR [5]. A GFR less than 60 mL/min/1.73 $m^2$ is an independent risk factor for heart failure. The mortality rate for patients with ESRD is more than 20% per year, making the prevention of cardiovascular complications the utmost priority [38].

Prevention strategies must start as early as possible. The vast majority of patients with ESRD have diabetes and hypertension, and patients with these diseases are already at high risk for developing CAD. Cardioprotective measures should begin at the time of the diagnosis of these diseases, not after end-organ damage has appeared. Unfortunately, 70% of patients who begin dialysis treatment already have left ventricular hypertrophy and 40% have congestive heart failure (CHF) [38; 39]. Clearly, improvements can be made in addressing cardiovascular complications early in the treatment of patients with renal disease.

***Hypertension***

Adequate blood pressure control has been proven beneficial in patients diagnosed with CKD [38]. Ideally, blood pressure should be reduced to less than 130/85 mm Hg [9]. The United Kingdom Prospective Diabetes Study showed benefit of even lower systolic pressures, with reduction in macrovascular complications in patients with diabetes continuing to systolic pressures as low as 114 mm Hg [40]. The use of ACE inhibitors and ARBs has also been shown to be beneficial in patients with diabetic nephropathy and for those with nondiabetic renal disease and proteinuria [40; 41; 42; 43; 44; 45; 46]. A meta-analysis suggested that ACE inhibitor therapy may provide superior benefit over ARB therapy, with a 10% reduction in all-cause mortality [47]. However, the selection of one agent over another will also take into account patient-specific factors (e.g., cost, potential for side effects). Simultaneous treatment with an ACE inhibitor and an ARB is not recommended, as this has been shown to worsen kidney function [6; 48; 49; 50; 51]. ACE inhibitors and ARBs should be used cautiously in patients at risk for hyperkalemia and should be avoided in patients with renal artery stenosis unless prescribed by a renal specialist, in which case close monitoring of renal function is absolutely essential [18; 32].


In adult patients with stages 1 through 4 chronic kidney disease, the Department of Veterans Affairs Guideline Panel suggests intensive blood pressure management beyond a target of less than 140/90 mmHg, to reduce mortality in patients with estimated glomerular filtration rate below 60 mL/minute/1.73 $m^2$.

(https://www.healthquality.va.gov/guidelines/CD/ckd/VADoDCKDCPGFinal5082142020.pdf. Last accessed November 21, 2024.)

**Strength of Recommendation**: Weak for

It is necessary to repeat serum potassium, BUN, and serum creatinine measurements one week after initiation of ACE inhibitor and/or ARB therapy. In addition, careful blood pressure monitoring is important, both to ensure control of hypertension (with a maximum blood pressure of 130/80 mm Hg) and to guard against hypotensive responses to ACE inhibitor therapy. For patients unable to tolerate ACE inhibitors and/or ARBs, the direct renin inhibitor aliskiren may be considered, but only for patients with stage 1, 2, or 3 CKD [52]. Studies are underway to explore the potential renal protective effects of aliskiren. Although it has been found effective in controlling hypertension, evidence suggests that it provides no benefit to patients with diabetes and cardiovascular disease or cardiovascular risk [53; 54]. Any patient requiring more than two to three drugs to control their hypertension should have an evaluation for secondary hypertension.

EVIDENCE-BASED PRACTICE RECOMMENDATION

The Department of Veterans Affairs Guideline Panel recommends against the use of combination renin-angiotensin-aldosterone system blockade (ACE inhibitor and ARB with or without a direct renin inhibitor) in patients with chronic kidney disease.

(https://www.healthquality.va.gov/guidelines/CD/ckd/VADoDCKDCPGFinal5082142020.pdf. Last accessed November 21, 2024.)

**Strength of Recommendation:** Strong against

Thiazides are recommended for patients with stage 1, 2, or 3 CKD and have been established as effective agents for reduction of blood pressure and risk of cardiovascular disease. Loop diuretics are recommended for patients with stage 4 or 5 CKD. These agents have been shown to be more effective in reducing extracellular fluid volume in patients with severely reduced GFR. It is important to note that the long-term effects of loop diuretics on cardiovascular outcomes have not been clearly established [55; 56; 57].

The simplest way to start a secondary hypertension work-up is to assess the patient's aldosterone/plasma rennin activity ratio, which can identify or rule out primary hyperaldosteronism. Patients with hypertension and hypokalemia (either without the use of diuretics or out of proportion to the dosage) should be considered at risk of having primary hyperaldosteronism (also referred to as Conn syndrome) [58]. A ratio greater than 20 to 30 ng/dL per ng/mL/hour is suggestive of this disease, requiring referral to a specialist for further evaluation and treatment [58].

Patients with a history of multiple endocrine neoplasm syndromes or those with symptoms suggestive of a pheochromocytoma (e.g., panic attacks, flushing, and labile hypertension) should have 24-hour urine collection to measure urinary catecholamines and fractionated metanephrines. Urinary vanillylmandelic acid was previously also measured (and still can be) but is felt to have both poor sensitivity and specificity [59].

### *Hyperlipidemia*

Hyperlipidemia is both a complication of CKD and a potential factor in the progression of the disease [9]. Lowering LDL cholesterol to achieve National Cholesterol Education Program goals (i.e., LDL less than 70 mg/dL) in patients with CKD is recommended [60]. The LDL target for any patient with diabetes and CKD is the same as for a patient without diabetes. A number of agents are available for the treatment of lipid disorders, although most have dosing limitations dependent on the degree of renal impairment present.

### *Healthy Behaviors*

For patients with CKD or ESRD and existing CAD, cardiac rehabilitation programs should be considered. Properly prescribed and monitored walking programs can achieve many goals, including weight loss, increased endurance, improved mental health, and increased socialization. Smoking cessation is also of critical importance. Many strategies exist, but the best approach is to talk to patients about smoking cessation, assessing for motivational stage (e.g., precontemplation, contemplation, action) and, if appropriate, referring to an addiction specialist or developing a plan of care with the patient. The plan should include listing benefits of quitting, motivations, aids to quitting (both pharmacologic and nonpharmacologic), a firm quit date, and a plan to decrease intake prior to the quit date. The patient should also have a return appointment scheduled to assess the adequacy of the plan, with continued follow-up appointments. Patients should be reminded that most smokers attempt to quit several times before being successful [61].

## Dietary Management and Metabolic Complications

An essential component of renal disease management is diet modification and dietary referral is beneficial for optimum care. This is especially true in patients with underlying diabetes and in patients who are under- or overweight, as the dietary recommendations must be modified in these cases. The American Dietetic Association has

established guidelines for renal failure diets, which are published in the Manual of Clinical Dietetics (***Table 4***) [42].

### *Protein*

Elevated protein catabolism and protein malnutrition are common in patients with CKD and ESRD [62]. Although protein restriction is widely recommended for patients with CKD or ESRD, the level of restriction remains controversial [63]. Limiting protein intake to 0.6–0.8 g/kg/day is generally accepted; however, guidelines for patients on hemodialysis recommend higher protein intakes of 1.2 g/kg/day [9; 64]. The Kidney Diseases Outcome Quality Initiative (KDOQI) guidelines recommend that patients with GFR <60 mL/min/1.73 $m^2$ undergo assessment of dietary protein, energy intake, and nutritional status [9]. It is important to monitor nutritional status via measurement of serum albumin and total protein [4; 9; 17; 42; 64]. A statistical correlation has been established between increased mortality rates and patients who initiate dialysis with low serum albumin and total protein levels [4; 17]. Although this relationship has been established only as a temporal and not a causal relationship, maintaining serum albumin and protein levels within normal limits would appear to be prudent management [9].

EVIDENCE-BASED PRACTICE RECOMMENDATION

In the adult with stage 3–5 CKD and diabetes, the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative asserts it is reasonable to prescribe, under close clinical supervision, a dietary protein intake of 0.6–0.8 g/kg body weight per day to maintain a stable nutritional status and optimize glycemic control.

(https://www.ajkd.org/article/S0272-6386(20)30726-5/fulltext. Last accessed November 21, 2024.)

**Level of Evidence**: Expert Opinion/Consensus Statement

**DIETARY RECOMMENDATIONS FOR ADULT PATIENTS WITH CHRONIC RENAL FAILURE WHO ARE NOT ON DIALYSIS**

| Nutrient | Recommendation |
|---|---|
| Protein | 0.6–0.8 g/kg/day |
| Calories | 35 kcal/kg/day |
| Phosphorus | 0.8–1.2 g/day |
| Calcium | 1.2–1.6 g/day |
| Sodium | 1–3 g/day |
| Potassium | <60 mEq/day (restricted if serum potassium level is elevated or urinary output is <1 L/day) |

*Source: [42]* *Table 4*

### *Blood Glucose*

Studies have shown the benefits of tight glycemic control in halting or slowing the progression of diabetic renal disease [4; 17; 18]. HbA1c levels within 10% of normal have been shown to be highly protective and associated with a lack of target organ damage [18; 32]. However, as discussed, studies have shown an increase in morbidity in the elderly with tight controls [36]. It may be prudent for older patients to maintain HbA1c levels no lower than 6%.

### *Potassium*

Although hyperkalemia is not usually a major issue in mild-to-moderate renal failure, monitoring of serum potassium (especially in patients taking ACE inhibitors or ARBs) is mandatory. Patients receiving ACE inhibitor therapy may require decreased dosages to maintain serum potassium within normal limits. ACE inhibitor-induced hyperkalemia may lead to necessary discontinuation of the medication. Most patients should be instructed to avoid potassium-containing salt substitutes, a supplement commonly used by hypertensive patients on sodium-restricted diets. Dietary potassium should also be limited to less than 60 mEq/day [42]. If necessary, sodium polystyrene (Kayexalate) should be prescribed to maintain healthy serum potassium levels (less than 6 mEq/L). It should be noted, however, that sodium polystyrene use may result in a clinically significant increase in sodium intake at higher doses.

### *Phosphorus and Calcium*

Control of serum phosphorus and calcium is crucial in preventing metabolic complications associated with CKD and ESRD. Many patients with CKD ultimately develop secondary hyperparathyroidism and renal osteodystrophy, even though these are often preventable entities. Therefore, patients should be instructed to limit dietary intake of phosphorus, which is found mainly in protein-rich foods like meat, dairy products, and nuts. Diets low in phosphorus (i.e., 0.8–1.2 g/day) have been shown to delay the progression of renal failure, probably as a result of the prevention of phosphate and calcium deposits in the interstitium of the kidney [65].

In addition to limiting intake of phosphorus, patients with renal failure require supplemental calcium. Calcium taken with meals binds to and helps decrease absorption of phosphorus, and calcium taken between meals helps raise serum calcium levels [17]. The normal starting dosage of elemental calcium is usually 600 mg twice daily with meals; this can be adjusted on the basis of ionized calcium values, iPTH, and serum phosphorus. When attempting to raise serum calcium levels, it is important that supplements be taken on an empty stomach, as an acidic environment is necessary for adequate absorption. The use of proton pump inhibitors to treat gastroesophageal reflux or peptic ulcer may prevent patients from adequately absorbing calcium. Another factor that may prevent the proper absorption of calcium is low vitamin D levels.

### *Vitamin D*

Vitamin D insufficiency has only been recently recognized as a major problem in CKD. The NKF guidelines issued in 2003 only call for monitoring vitamin D levels (via measurement of 25(OH) D levels) in patients with elevated PTH. However, more recent studies on vitamin D and mortality have led to the routine monitoring of 25(OH) D levels in all patients with CKD [66]. Both the KDOQI and KDIGO recommend assessing and supplementing low serum 25(OH)D levels in patients with CKD and those on dialysis. Replacement therapy should aim to maintain 25(OH) D levels of at least 25 ng/mL, and some clinical laboratories have set reference values at 30–60 ng/mL; however, this remains controversial because of a lack of consensus regarding the optimal range for serum 25(OH)D [9; 67; 68; 69; 70; 71]. When prescribing vitamin D, it is important to understand that it is produced both as vitamin D2 (ergocalciferol from vegetable sources) or vitamin D3 (cholecalciferol from animal sources). Vitamin D3 must still be hydroxylated in the kidney to calcitriol, but it is felt to be the more potent of the two formulations. The biologically active form of D3 is calcitriol, but the use of prescription calcitriol is only necessary in advanced renal disease (i.e., GFR rates less than 30 mL/min/1.73 $m^2$), as these patients lack the ability to synthesize 1,25-dihydroxyvitamin D. Concurrent use of aluminum or magnesium antacids should be avoided.

### *Medication Metabolism*

Alterations in metabolism and renal function are present in many patients with CKD, and many drugs must be avoided or adjusted on the basis of renal function (***Table 5***). When any drug is prescribed for a patient with CKD, manufacturer's recommendations regarding use in the presence of renal disease should be determined. Decisions may be made based on creatinine clearance, which may be estimated with the following equation:

Creatinine clearance = (140 - age) ÷ weight [kg]/72 × serum creatinine (mg/dL) × (ideal weight [kg] ÷ 72) (× 0.85 if female)

However, a newer calculation to estimate GFR from serum creatinine has been developed. The isotope dilution mass spectrometry (IDMS)-traceable Modification of Diet in Renal Disease Study equation takes into account race, age, and gender [72; 73]. Also referred to as the eGFR, many diagnostic laboratories are offering to list the result automatically when measuring serum creatinine. This measurement is based on the following equation:

$$eGFR = 170 \times \text{serum creatinine (mg/dL)}^{-0.999} \times \text{age}^{-0.176} \times \text{BUN}^{-0.170} \times \text{albumin}^{0.318}$$ (x 0.762 if female) (x 1.180 if African American)

| DRUGS REQUIRING DOSAGE ADJUSTMENT IN CHRONIC RENAL FAILURE[a] |
|---|
| Antibiotics |
| NSAIDs |
| Digoxin |
| Phenobarbital |
| Opioids |
| Antiarrhythmics |
| Antihypertensives |
| Antifungals |
| Antivirals |
| Librium |
| Lithium carbonate |
| [a]Always consult the manufacturer's instructions when prescribing any drugs for patients with chronic renal failure. |

*Source: Compiled by Author* *Table 5*

In 2021, the National Kidney Foundation (NKF) and the American Society of Nephrology (ASN) convened a task force to focus on the use of race when estimating GFR. This task force recommends the CKD-EPI creatinine equation, a race-free approach to measuring eGFR [74; 75]. For more information and to view the calculator, visit https://www.kidney.org/professionals/KDOQI/gfr_calculator [75].

### Hematologic Management and Complications

Erythropoietin production is usually normal in patients with GFR rates greater than 20 mL/min/1.73 $m^2$. However, the CBC should be monitored. If the hematocrit level falls to less than 32% (the level at which erythropoietin production is stimulated), serum erythropoietin levels should be assessed to determine the cause of the anemia. If serum erythropoietin stays low, exogenous erythropoietin should be given. To avoid transfusion-related hepatitis B (as well as the need for increased infection control precautions during hemodialysis), immunization should be given to patients who are antibody negative. Follow-up serology (i.e., hepatitis B surface antibody and hepatitis B surface antigen) should also be obtained, as many uremic patients seem to have problems mounting a demonstrable immune response after immunization [76].

EVIDENCE-BASED PRACTICE RECOMMENDATION

The Department of Veterans Affairs Guideline Panel recommends against offering erythropoiesis-stimulating agents to patients with chronic kidney disease for the purpose of achieving a hemoglobin target greater than 11.5 g/dL due to increased risk of stroke and hypertension.

(https://www.healthquality.va.gov/guidelines/CD/ckd/VADoDCKDCPGFinal5082142020.pdf. Last accessed November 21, 2024.)

**Strength of Recommendation**: Strong against

### Psychosocial Management

Although the medical management of CKD may seem overwhelming to even veteran healthcare providers, it is often devastating to patients. Therefore, it is essential to provide adequate social and psychiatric support.

#### *Grief and Sorrow*

Loss, sorrow, and the ensuing grief are characteristic in patients coping with chronic illness [17]. There is grief of the loss of a body part and of physical functioning [34]. Variables such as age, gender, health before the diagnosis of the illness, and the patient's existing social support influence what types of losses will be experienced [17]. Both the patient and family members grieve and mourn over the loss of the person who once was and the personality and traits associated with that person [35]. This process has been referred to as chronic sorrow, because although the patient may have accepted the diagnosis, the feelings of grief and loss continue to wax and wane throughout the course of the illness [36]. One interview study found that advance care planning provides patients with ESRD and their caregivers who may be experiencing overwhelming grief a conduit for overcoming personal and decisional conflict [77].

### *Depression*

As previously noted, there is a significant association between depression and CKD, with studies indicating that 14% to 45% of patients with CKD have symptoms of major depressive disorder [78; 79]. In a study of 267 patients with CKD who were not receiving dialysis, the presence of depressive symptoms was a predictor of poor outcomes independent of functional status and disease severity [80]. Evidence of the safety and efficacy of available antidepressants in the presence of impaired renal function is insufficient but suggests benefits with treatment [78].

Major predictors of compound depression in patients with CKD include baseline cognitive impairment, functional disability, and other chronic illness [81]. Because functional disability will have greater socioeconomic impact in lower income populations, this group may be at increased risk for developing depressive symptoms.

Because depression is so prevalent among patients with CKD, nephrologists and primary care providers should consider assessing for depressive symptoms among their patients, especially among those with worse functional statuses. Research indicates that communication with patients with CKD regarding depressive symptoms is a key aspect of identifying and effectively treating the condition before it becomes more severe. Despite its known importance, depression continues to be underdiagnosed and undertreated in patients with CKD. In one study, primary care nurses were significantly more likely to identify depression in patients on long-term hemodialysis than the nephrology team, indicating that improvements in this area are needed [82].

### *Socioeconomic Impact*

Referral to a social worker can help in providing social support, locating resources, and applying for financial assistance and entitlement programs. Even with Medicare coverage, the costs of renal disease can be devastating, and many patients with CKD are unable to continue working because of medical complications [83].

## STAGE 4: SEVERE RENAL DISEASE

When GFR falls to less than 20 mL/min/1.73 $m^2$, the progression to ESRD is virtually inevitable [31]. Because prevention of progression is improbable, the focus of management switches to prevention of complications. Although continued control of complications and metabolic/dietary concerns is important, the goals become more difficult as the GFR approaches 10 mL/min/1.73 $m^2$. Consultation with a renal specialist is imperative for proper care and planning at this point, and ideally, a relationship will have already been established.

### Cardiovascular Management and Complications

Despite careful management, cardiovascular complications and management issues will develop in patients with severe renal disease. The onset of CHF and pulmonary edema may indicate the need for dialysis. Hypertension may escalate, and increasingly higher doses of both diuretics and antihypertensive medications are often necessary. The evidence for stopping ACE inhibitors or ARBs at times of high risk for acute kidney injury is not clear and the decision should be individualized based on considerations such as the patient's hemodynamic status. For patients with progressive CKD, the evidence indicates that ACE inhibitors or ARB should be continued until kidney replacement therapy is commenced [31]. The addition of sodium polystyrene can allow for continued use of these drugs, but its use may be contraindicated for hypertensive patients. Hypertension is often volume dependent, and increasing doses of diuretics may be needed. It is important to consider the patient's weight, serum BUN, serum creatinine, and clinical presentation when monitoring diuretic therapy; removing too much volume can easily trigger prerenal AKI. Furthermore, due to decreased kidney metabolism, the half-life of furosemide rises dramatically and ototoxicity can become an issue.

### *Nephrogenic Systemic Fibrosis*

The use of gadolinium-based contrast medium in renal failure patients dramatically increases their risk for nephrogenic systemic fibrosis. Gadolinium dyes are typically used in magnetic resonance imaging (MRI) to aid in the visualization of abnormal vascularity. The FDA has published guidelines for the appropriate use of these dyes specific both to the patient's level of renal function and the particular brand of dye being used [84]. Only physicians trained in the use of contrast medium should prescribe these products. However, healthcare providers involved in the care of patients with renal disease, especially those working in the catheterization lab or radiology, should familiarize themselves with the standards set forth by the FDA. Furthermore, all patients should be informed of the risks and benefits of the administration of these contrast mediums. This topic will be discussed in more detail later in this course.

### Dietary Management and Metabolic Complications

The KDOQI guideline for nutrition in chronic renal failure states that "for individuals with GFR <25 mL/min who are not undergoing maintenance dialysis, the institution of a planned low-protein diet providing 0.60 g protein/kg/day should be considered" [9]. Controversy remains within the nephrology community as to the role of protein restriction, partly because of the previously mentioned correlation with lower serum albumin levels and higher mortality rates [4; 17]. The guideline further recommends a caloric intake of 35 kcal/kg/day for individuals younger than 60 years of age and 30–35 kcal/kg/day for individuals 60 years of age or older [9]. Nausea and vomiting may become problematic, and the use of high-calorie supplements may be necessary for these patients.

The maintenance of calcium and phosphorus values as close to normal range as possible is also important. Although restriction of salt and potassium may not have been previously necessary, these elements now must be restricted. Intact PTH levels should be monitored; levels two to three times normal can be expected, but levels above this range indicate the need for endocrinology referral. Cinacalcet (a calcimimetic) was approved in 2004 to treat secondary hyperparathyroidism in renal failure, which allows for the direct treatment of elevated iPTH levels. The starting dosage is 30 mg/day, with titration up to 180 mg/day, with target iPTH levels of 150–300 pg/mL [29]. While morbidity and mortality data has yet to be collected on the use of cinacalcet, it is hoped that by preventing hypercalcemia, its use may decrease the incidence of atherosclerotic disease in patients with CKD [85]. An analysis of the EVOLVE trial data set, while inconclusive, suggests a greater relative benefit of cinacalcet on nonatherosclerotic cardiovascular events, including sudden death and heart failure, than on atherosclerotic events [86]. However, due to the high cost, numerous payers have placed limits on reimbursement for its use [87].

### Hematologic Management and Complications

Erythropoietin levels are not routinely used in distinguishing erythropoietin deficiency from other causes of anemia in patients with CKD in most clinical settings and their measurement is generally not recommended by the KDIGO [60]. As in any disease state, pathological conditions that can be cured should be corrected first. For example, treatment with erythropoietin-stimulating agents (ESAs) is unlikely to be fully effective in raising hemoglobin concentrations until either severe systemic bacterial infections or severe secondary hyperparathyroidism are appropriately treated [60]. When initiating and maintaining ESA therapy, the KDIGO recommends balancing the potential benefits against the risks of harm in individual patients [60].

### Psychosocial Management

One of the major tasks for patients with severe renal disease in the failure phase is planning for dialysis. This can be traumatic for the patient, leading to depression or anxiety, but it is crucial for the prevention of major complications. Referral to a nephrologist is indicated if one has not already been made. The type of dialysis should be determined and the appropriate type of access established. AV fistulas take up to three months to heal and therefore should be placed well in advance. According to

the USRDS, more than 85% of patients presenting for initial hemodialysis have no permanent access and are dialyzed via temporary catheter [2]. If continuous ambulatory peritoneal dialysis or automated nighttime peritoneal dialysis is elected, training is required and should be started as early as possible. Patients should visit the dialysis unit that will be managing their care to familiarize themselves with both the routine and the staff.

As discussed, depression and suicide are major considerations, and every effort should be made to provide psychosocial support. Selective serotonin reuptake inhibitor antidepressants can be used, and the dosage does not have to be adjusted for CKD. If transplantation is a possibility, discussions regarding this issue can begin at this point.

## STAGE 5: END-STAGE RENAL DISEASE

ESRD is commonly defined as a GFR of less than 15 mL/min/1.73 $m^2$, and the basic hallmark of ESRD is uremia [5; 88]. Uremic toxins are the byproducts of protein metabolism; in patients with ESRD, the toxins are not eliminated by the kidneys and begin to accumulate [5]. Severe uremia necessitates the use of dialysis to remove uremic toxins and prevent or control complications.

Symptoms of uremia affect virtually all major body systems and can include drowsiness, obtundation (that can evolve into coma), peripheral neuropathy, restless legs syndrome, atherosclerosis, cardiomyopathy, pulmonary edema, pneumonitis, anorexia, enterocolitis, pancreatitis, ascites, pruritus, anemia, platelet dysfunction, insulin resistance, and hyperlipidemia [5]. BUN levels are markers of uremia. Normal BUN levels range from 7–20 mg/dL. In patients with ESRD, BUN may rise to levels greater than 100 mg/dL. The most useful BUN measurement is the ratio of BUN to serum creatinine, which in healthy patients ranges from 0.5–1.2 mg/dL, dependent on muscle mass. Therefore, the normal BUN to serum creatinine ratio is 20:1. Higher ratios reflect dehydration. However, initiation of dialysis should be guided not just by laboratory values but also by clinical presentation. The presence of uremic symptoms in the patient, especially sleepiness and changes in mental status or serious complications such as pancreatitis or pulmonary edema, should be a major consideration when making treatment choices [88].

### Cardiovascular Management and Complications

Hypertension and hyperlipidemia should continue to be aggressively managed in patients with ESRD. Whereas the renal specialist may be concerned with fluid and electrolyte balance, primary care providers should consider the potential for cardiovascular complications, as these are leading causes of death in patients with ESRD [4; 88].

Pulmonary edema and CHF are major concerns in ESRD. If the patient is unstable, hospitalization and urgent dialysis may be necessary. All episodes of CHF and pulmonary edema should be reported to the renal specialist so adjustments can be made in the dialysate to compensate for fluid overload.

### Dietary Management and Metabolic Complications

Dietary management of patients with ESRD should be aimed at control of electrolytes (including calcium, phosphorus, and potassium), prevention of malnutrition, and maintenance of acceptable fluid volume status [9]. Daily dietary requirements for patients with ESRD depend on the type of dialysis chosen (i.e., continuous ambulatory peritoneal dialysis or hemodialysis). The American Dietetic Association has published specific nutrition guidelines for patients who are on continuous ambulatory peritoneal dialysis or hemodialysis (***Table 6***). Adults with normal renal function can generally eat large amounts of protein and maintain BUN levels without symptoms [5]. However, most patients with ESRD will require a protein-limited diet. All patients with ESRD should be referred to a dietitian for optimization of nutritional status.

| DIETARY RECOMMENDATIONS FOR ADULTS WITH END-STAGE RENAL DISEASE ON DIALYSIS | | |
|---|---|---|
| **Nutrient** | **Recommendation for Hemodialysis** | **Recommendation for Peritoneal Dialysis** |
| Protein | 1.1–1.4 g/kg/day | 1.2–1.5 g/kg/day |
| Calories | 30–35 kcal/kg/day | 25–35 kcal/kg/day |
| Phosphorus | <17 mg/kg/day | <17 mg/kg/day |
| Calcium | 1.0–1.8 g/day | 1.0–1.8 g/day |
| Fluid | Daily urinary output + 500–750 mL/day | 2–3 L/day based on weight and blood pressure |
| Sodium | 2–3 g/day | 3–4 g/day based on weight |
| Potassium | 40 mg/kg | Unrestricted unless elevated |
| *Source: [42]* | | *Table 6* |

While the impact of chronic renal disease on the endocrine system is destructive and pervasive, the impact of uremic syndrome and ESRD is devastating to the endocrine system. There are at least eight different causes of endocrine system failure in uremic syndrome: diminished production of renal hormones, hormonal hypersecretion, decreased metabolic clearance of hormones, blunted feedback response, defective tissue conversion, decreased hormone production of nonrenal hormones, end organ unresponsiveness, and increased circulating inhibitors of hormones [5].

Diminished production of renal hormones includes both decreased secretion of erythropoietin and decreased conversion of 25-hydroxyvitamin D3 to its active metabolite, 1,25 dihydroxyvitamin D3. To prevent anemia due to decreased erythropoietin, exogenous erythropoietin must be given, and the costs associated with this are high. As stated previously, erythropoietin levels are not routinely used in distinguishing erythropoietin deficiency from other causes of anemia in patients with CKD in most clinical settings and their measurement is generally not recommended by the KDIGO [60].

To prevent osteomalacias, secondary hyperparathyroidism (due to hypersecretion of parathyroid hormone), and possibly other organ damage, supplementation to treat low vitamin D levels is indicated in the presence of increased PTH levels. Several studies have also shown increased overall survival for patients on hemodialysis receiving highly active vitamin D3 formulations such as calcitriol and α-calcidiol [89; 90]. Calcidiol (calcifediol) is not recommended for patients with stage 5 CKD or patients with ESRD on dialysis [29]. It should be reserved for patients with secondary hyperparathyroidism [88]. It is important to use cholecalciferol (D3) as opposed to ergocalciferol (D2) in patients with ESRD, as it is the active hormone and does not need further metabolism in the kidneys [88].

End organ resistance to stimulating hormones is evidenced by growth retardation in uremic children, but the exact process by which the hormone is unable to properly stimulate growth has yet to be discovered. Resistance to insulin in uremic patients is well documented, and uremic patients typically have higher blood sugar levels, despite impaired removal of circulating insulin by the kidneys. Again, exact pathways of resistance are not understood.

**Hematologic Management and Complications**

Erythropoietin replacement therapy will be necessary for nearly all patients on dialysis. Erythropoietin given subcutaneously is more effectively absorbed than erythropoietin given intravenously (or into extracorporeal blood during hemodialysis); however, patients may favor the convenience of receiving erythropoietin during their dialysis treatment without having to receive an extra injection.

When given IV during dialysis, higher doses of erythropoietin are needed, leading to higher costs. Therefore, some payers have required patients to remain on subcutaneously administered erythropoietin even after initiation of dialysis. Also, in 2011 the FDA recommended more conservative dosing of epoetin alfa and other ESAs in patients with CKD [91]. In their statement, the FDA asserted that ESA therapy should be individualized to the patient and the lowest possible ESA dose given to reduce the need for transfusions.

### Use of Diuretics

There are many different classes of diuretics, with different sites of action and different elimination pathways. While the choice of diuretic may be simple in mild-to-moderate disease, it becomes more complicated and important as the disease becomes more severe and dialysis is considered.

Loop diuretics are probably the type most familiar to clinicians and include furosemide, bumetanide, and torsemide. Loop diuretics act in the thick ascending limb of the loop of Henle, but their elimination sites vary. Furosemide undergoes a "first pass" in the kidney, and normally half of the drug is metabolized to its inactive state (glucuronide) here. Only the inactivated fraction is available to inhibit sodium chloride reabsorption, and therefore, it can have a prolonged half-life in patients with GFRs of less than 20–30 mL/min/1.73 $m^2$. While this may actually help increase its potency, in high doses it can lead to ototoxicity.

Patients often develop resistance to a particular class of diuretics. This may be the result of changes in the tubules, so adding a diuretic with a different site of action may help. While spironolactone is often prescribed for liver failure patients with renal involvement, it must be used carefully, as hyperkalemia is a potentially serious complication of its use. Of more use in renal failure may be the thiazide and thiazide-like diuretics, such as metolazone, that work in the distal convoluted tubule. Combining metolazone with a loop diuretic may help minimize the need for very high doses of furosemide, thereby decreasing side effects such as ototoxicity.

### Psychosocial Management and Complications

The stress of dealing with severe chronic illness can be psychologically devastating. Patients with ESRD (especially patients on hemodialysis) are known to suffer from high rates of depression, insomnia, and anxiety [92]. Often ignored, sexual dysfunction occurs at high rates in both male and female patients with ESRD [92]. The treatment of these and other psychiatric complications should begin before the onset of ESRD, when possible, and continue as long as necessary.

## INDICATIONS FOR REFERRAL OR HOSPITALIZATION

All patients with CKD should be referred as early as possible to a renal specialist for consultation. If a dietitian is available, referral should be made as well. Hospitalization should be considered for any acute, life-threatening disorder or complication. More common causes include acute fluid and electrolyte disorders, acute hypertensive emergency, pulmonary edema, acute CHF, pericarditis, and metabolic acidosis.

# DIALYSIS

There are two major types of dialysis currently in use in the United States: hemodialysis and peritoneal dialysis. Though generally used for patients with ESRD, it may also be a short-term option in the treatment of patients with AKI or in post-transplant patients with delayed graft function. In 2021, 113,309 patients initiated in-center hemodialysis, representing 83.8% of individuals with incident ESRD. This was a decrease from a peak of 91.4% in 2008 [11]. Despite this large number, dialysis is a relatively new therapy and has only been routinely provided for approximately 40 years [5].

## HISTORY

The basis for dialysis was not established until the discovery of diffusion and osmosis in the 1800s. This early form of chemical dialysis was initially used only in laboratories to separate chemical compounds.

Thomas Graham and Adolf Fick established some of the first formal chemical procedures for separating chemical substances using diffusion across semipermeable membranes to separate dissolved substances. The formal theoretical foundation for dialysis was established by Albert Einstein when he described diffusion laws deriving from thermodynamics and Brownian molecular motion [5; 93].

Hemodialysis uses an extracorporeal semipermeable membrane to separate uremic substances from the blood of patients suffering from kidney disease. The first known occurrence of the use of an extracorporeal filter was in 1913 on anesthetized animals [5; 93]. Although crude, this technique of extracorporeal filtration remains the basis for current hemodialysis. The first human experiments were performed in Germany by George Haas in 1924. None of his patients survived, but all were in critical condition and were not expected to survive at the time of the procedure. One of the major contributions of Haas' experiments was the introduction of heparin as the anticoagulant of choice to prevent clotting in the filter mechanism; previous experiments had used a leech-based derivative [5; 93].

The first successful hemodialysis on a living patient was accomplished by Willem Kolff in 1945 in the Netherlands. After 16 failures, he successfully dialyzed a woman 67 years of age suffering from acute renal failure using a rotating drum artificial kidney [5; 93].

Although approximately 84% of patients on dialysis in the United States receive hemodialysis, peritoneal dialysis is also an option, and in some countries (including Mexico, New Zealand, and Australia), it is the major form of outpatient dialysis [94]. The decision to implement peritoneal dialysis rather than hemodialysis can be affected by many nonclinical factors, such as reimbursement, government policies, physician preference, and available expertise [5; 11; 65].

The first known clinical use of peritoneal dialysis occurred in 1923, and by 1950, at least 100 patients had been treated, most of whom were in acute failure. Of these patients, 32 successfully regained normal function [5]. However, continuous ambulatory peritoneal dialysis was not formally described until 1976. In continuous ambulatory peritoneal dialysis, the peritoneum acts as the semipermeable membrane and dialysis fluid is introduced via a permanent catheter, with old fluid removed and new fluid introduced either automatically during the night via an automated system (continuous cycler-assisted peritoneal dialysis) or manually up to four times per day (continuous ambulatory peritoneal dialysis) [65].

Peritoneal dialysis differs from hemodialysis in several ways. First, the membrane itself is not customizable; the patient's peritoneum is genetically determined. Secondly, the catheter transverses both a nonsterile (exterior abdomen) and sterile (peritoneum) environment. Thirdly, peritoneal dialysis solutions must be delivered to the home and used by patients and families. These difficulties have historically resulted in a relatively low rate of peritoneal dialysis use in the United States [5; 65].

Use of home dialysis was 0.4% in 2021 and has been relatively stable since 2001 In 2021, use of peritoneal dialysis was 37.8% higher than in 2001 [11]. Peritoneal dialysis has continued to be the dominant form of home dialysis. As stated, approximately 83.8% of patients on dialysis in the United States continue to be treated by in-center hemodialysis [11]. This results in many nephrologists having little experience with peritoneal dialysis, creating a difficult-to-break cycle of lack of use due to lack of experience.

## ACCESS

### Hemodialysis

Planning for access should occur well before the need for dialysis, as proper access may take months to properly heal. As previously mentioned, more than 85% of patients presenting for initial dialysis are dialyzed via temporary venous catheters due to a lack of established access [11].

Hemodialysis can be provided via three major different types of access: an AV fistula, an AV graft, or a temporary venous catheter. In its 2006 guideline for vascular access, the NKF endorsed a goal for at least 65% of all patients on hemodialysis to have a working AV fistula by 2009 [95]. In the 2019 update of the guideline, the vascular access Work Group emphasizes a more patient-focused approach that takes into account each patient's needs and preferences when choosing access type [96]. From 2012 to 2022, the percentage of institutions initiating hemodialysis with an AV fistula fell from 16.5% to 12.5% [11].

AV fistulas are created surgically by attaching an artery directly to a vein. Generally placed in the forearm, AV fistulas may be categorized as radial-cephalic, brachial-cephalic, or brachial-basilic based on the vein and technique used [5; 97]. Generally, the radial-cephalic, having a lower anatomical position in the forearm, is preferred for first access as it preserves the higher veins for later use. After anastomosis, the resultant increase in blood flow to the vein results in thickening of the venous wall, allowing it to withstand the numerous punctures required for hemodialysis [97]. AV fistulas generally require at least three months to fully mature. AV fistulas are recommended as the first form of access, and they should be promoted in all eligible patients who choose hemodialysis, as they improve outcomes and reduce costs compared with central venous catheters [98]. They also offer the best access for longevity and have the lowest association with morbidity and mortality [99]. However, multiple studies suggest that certain subgroups of patients (i.e., the elderly and those with limited life-expectancy) may benefit from alternative forms of access. As stated, a patient-centered, individualized approach to the choice of access may indicate the use of a method other than AV fistula [96; 100; 101].

AV fistulas are not without complications, and the overall patency rate is only 50% after five years [97]. Fistula failure can be classified as early (in the first three months) or late (after three months) [97]. Early failure is generally due to infection, stenosis, or obstruction (either of inflow or outflow). Late failure is generally due to either venous stenosis or arterial lesions, with venous stenosis being the most common cause of late AV fistula failure [5; 97]. Steal syndrome is another possible complication of AV fistulas and results in too high of a diversion of blood flow from the extremity distal to the fistula. It occurs most commonly after brachial artery-based AV access, although it can occur after radial artery-based or lower-extremity access [96]. Patients with steal syndrome may present with signs and symptoms of decreased blood flow to the affected extremity, particularly in the digits of the hand. Patients at high risk of steal syndrome who may benefit from mitigation strategies include older patients, women, patients with diabetes or peripheral vascular disease, those who have had multiple prior permanent access procedures, and those who have experienced a prior episode of AV access steal [96]. Treatment of this complication includes the takedown of the fistula or placement of coils in the fistula to decrease diversion. Patients deemed at risk for imminent limb or digit loss should be referred immediately to the emergency department for evaluation by a vascular surgeon.

Fistula patency can be assessed by palpation of "thrill" and auscultation of bruit. A palpable motion in the surface of the fistula and a bruit when a stethoscope is placed over the fistula should both be present. The bruit should be loudest at the arterial side of the fistula. Patients found to have nonpatent grafts should be referred immediately to interventional radiology, as patency can often be restored by the use of antithrombotics (e.g., tissue plasminogen activators) and/or balloon angioplasty. Unfortunately, the use of contrast medium is usually necessary in order to restore patency. In these cases, the patient should be dialyzed within 24 hours of receiving the contrast. If the patient is to receive dialysis immediately after angioplasty, catheters may be left in place so it is not necessary to recannulate immediately after the procedure. If the patient is to return the following day for dialysis, temporary

catheters should be removed to prevent potentially deadly hemorrhage. At no point should any patient with ESRD receive gadolinium-based contrast dye due to the risk of nephrogenic systemic fibrosis [96]. Postexposure dialysis does not decrease the risk of developing nephrogenic systemic fibrosis in at-risk patients.

AV grafts are generally considered to be inferior to AV fistulas and superior to temporary catheters, but fewer than half are patent after five years [102]. These grafts are often used for patients who lack veins large enough to create fistulas. The determination of need for graft placement versus fistula is accomplished via vein mapping and clinical evaluation.

AV graft formation is accomplished by implantation of a synthetic tube that connects a vein and an artery. Dialysis is then performed by cannulating the synthetic graft. Synthetic grafts have higher rates of infection and clotting and, as noted, generally fail sooner than fistulas [103].

Both AV fistulas and grafts should be cannulated only by trained practitioners. Repeated same-site cannulation can result in destruction of grafts, aneurisms, and/or infiltrates. Although not all of these complications are entirely preventable, trained inserters can minimize their occurrence.

Temporary catheters are the least preferred method of access for hemodialysis, but one of the most frequently used. However, according to data from the Centers for Medicare and Medicaid Services, catheter use in the United States declined slightly from approximately 28.0% in 2006 to 17.4% in 2017 [104]. Central venous catheters for dialysis (CVCDs) are generally tunneled catheters with two external access ports ("pigtails") and a tunneled lumen under the skin that extends into the vena cava; they may last up to one year. The introduction of advanced CVCDs has helped make temporary catheters a viable solution for patients with very poor vascular status. Patients often prefer the temporary catheters to other forms of access, as they do not involve the pain of subcutaneous cannulation and are often cosmetically more acceptable. Using a tunneled catheter helps reduce the risk of infection but does not eliminate it.

### Peritoneal Dialysis

The peritoneal catheter is the only option for peritoneal dialysis. The invention of the Tenckhoff catheter in 1968 helped reduce high rates of peritonitis associated with peritoneal dialysis. It is made of silicone rubber and Dacron cuffs and can be coiled or straight. Compared with coiled cuffs, straight cuffs have higher catheter survival and fewer complications [105]. Coiled catheter use has been associated with lower rates of failure due to outward migration of the catheter [106; 107]. Most catheters in use today have two cuffs: one in the musculature of the abdominal wall and one in the subcutaneous tissue nearer the exit. Placement is generally performed operatively and can now be accomplished laparoscopically. Other methods, such as blind insertion via Tenckhoff trocar or guidewire, are available.

After insertion, approximately 7 inches of catheter extend beyond the surface. The catheter will usually have an external suture in place for the first two weeks after implantation. An external flow switch that is capped when not in use is present at the end of the catheter.

## COMPLICATIONS SPECIFIC TO PATIENTS RECEIVING HEMODIALYSIS

Hemodialysis is a risk factor for a variety of complications, and patients must be closely monitored. Mortality rates for patients with ESRD are high in part due to uncontrolled complications associated with dialysis.

Patients on hemodialysis often experience hypotension during and after dialysis sessions. A fluid gain of 4 or more liters between sessions is not uncommon, and this same amount of fluid must then be removed over a four-hour dialysis session. Most of this fluid is situated in the extravascular space, and dialysis removes fluid only from the intravascular space. So, changes in osmotic pressure between the intravascular and extravascular must allow for fluid movement during dialysis. If the patient becomes acutely hypotensive, the dialysis may need to be interrupted and the patient placed in Trendelenburg (supine) position with elevated feet. Rarely, fluid replacement may be required.

Cramping is also common, especially at the end of the dialysis session after large amounts of fluid and electrolytes have been removed. Severe cramping may require administration of normal saline. For patients who are significantly bothered by cramping, hydromorphone (Dilaudid) 1–2 mg orally may be given one hour before the usual onset of cramping. Hydromorphone has the advantage of not being dialyzed out of the patient's system.

## RENAL TRANSPLANTATION

Renal transplantation involves the surgical implantation of a kidney from either a living or deceased donor into the body of a patient with ESRD. Generally, candidates must have GFRs less than 20 mL/min/1.73 $m^2$. Transplants are classified as living donor related, living donor unrelated, or deceased (cadaveric) donor. The first truly successful human kidney transplant was in 1954 by Dr. Joseph Murray at Brigham Hospital in Boston. This first transplant involved identical twins, as anti-rejection medications had yet to be discovered. In the 1960s, tissue typing and anti-rejection drugs made the use of deceased donor kidneys and non-twin living donors possible.

In 1980, more than 3,000 kidney transplants were being performed annually. By 2013, this figure had risen to more than 17,600 [108]. Fewer than one-third of transplanted kidneys were from living donors in 2013. In 2021, the number of kidney transplants reached an all-time high of 25,549 [11].

The benefits of renal transplantation should not be underestimated. The survival of transplant patients is far higher than patients receiving dialysis. Some of this may be attributable to patient selection; healthier patients are selected for transplantation and terminally ill patients are rarely selected. Still, the statistics are impressive. At 91.5%, the five-year survival rate for transplant patients is more than twice the rate for patients receiving dialysis (40.7%) [11]. However, patient survival is not the same as donor graft survival. For the most recent years of data available, the probability of graft survival for living-donor transplants was 98%, 88%, and 79%, for 1-, 5-, and 10-year periods post-transplant, respectively [108].

### INDICATIONS AND CONTRAINDICATIONS

The indication for transplantation is ESRD, or a GFR of <15 mL/min/1.73 $m^2$ [9]. In recent years, the process for selection of kidney transplant has liberalized, with larger numbers of elderly patients being accepted for transplantation. In 1991, 30% of kidney transplant recipients were older than 50 years of age. In 2021, the rate of kidney transplantation is 42.3 per 100 person-years among individuals 0 to 17 years of age, 9.8 among individuals 18 to 44 years of age, 5.0 among individuals 45 to 64 years of age, 2.9 among individuals 65 to 74 years of age, and 0.5 among individuals 75 years of age or older. This distribution represented a slightly younger mix of transplant recipients compared to 2017 [11]. Guidelines for selection of patients for transplantation vary from program to program. Generally, metastatic disease or severe pulmonary or heart disease are exclusionary factors. Human immunodeficiency virus (HIV) is no longer considered an absolute contraindication, and studies have shown that patients with ESRD and HIV nephropathy have an increased life expectancy when treated with transplantation versus dialysis [109].

### ALLOCATION OF DONATED KIDNEYS

Allocation of all transplants in the United States is managed by the United Network for Organ Sharing (UNOS). Kidney transplant guidelines place the highest considerations on histocompatibility and time spent on the transplant list [110]. Children suffering from ESRD will lose growth (and possibly other milestones) while on dialysis, so they are given priority. The median adult wait time for a cadaver kidney is just over four years [108].

One result of this method of allocation is a potential mismatch of grafts and patients. If a patient with a life expectancy of 10 to 20 years receives a kidney from a donor who is/was 20 years of age (with a potential for 50 to 60 years of function), the transplanted kidney will potentially be underutilized. Worse, if a patient with a 40- to 50-year life expectancy receives a kidney from an older donor, he or she will likely outlive the donated kidney. In fact, approximately 14% of all patients awaiting transplantation have already received at least one transplant [11].

To address these problems and others, in 2021, the Organ Procurement and Transplantation Network (OPTN) (which operates under contract with the U.S. Department of Health and Human Services by UNOS) released a new policy for matching kidney transplant candidates with organs from deceased donors [111]. The new policy is "projected to increase equity in transplant access for candidates nationwide" by replacing "distribution based on donation service area and OPTN region with a more consistent measure of distance between the donor hospital and the transplant hospital for each candidate" [111]. Additional policy updates implemented at the same time involve allocation of kidneys from Alaska, prioritization of medically urgent patients, and how released kidneys are distributed in the new system when the original intended candidate is not able to be transplanted [111]. The OPTN projects that the new policies will improve transplant access for key groups of candidates, including children, women, ethnic minorities, and candidates who are particularly hard to match for biological reasons [111].

### SURGICAL TRANSPLANTATION

Transplanted kidneys are generally placed in the extraperitoneal space in the right iliac fossa. Pediatric patients can have their grafts placed in the intraperitoneal space. The major consideration for placement of the graft is surgical access to the renal arteries, renal veins, and the ureter. Failed kidneys are rarely removed unless infection or carcinoma is present. The donor's renal artery is usually anastomosed to the recipient internal iliac artery, and the donor renal vein is connected to the recipient external iliac vein. Lastly, the donor ureter is attached to the recipient bladder.

#### Postoperative Care of the Kidney Transplant Patient

Immediate postoperative care of the post-transplant patient involves all the usual issues involved in major surgery (e.g., bleeding, pain management, bowel function, infection, postoperative cardiac, pulmonary complications) as well as issues specific to the kidney transplant patient. These issues include graft function, acute rejection, urine leakage from the ureter anastomoses, and complications from immunosuppression. Acute rejection is not nearly the problem it was prior to the development of tacrolimus and cyclosporine, although chronic rejection remains a problem in long-term graft survival.

After transplantation, the graft may function immediately, have delayed graft function, or have complete non-function. Delayed graft function is a common problem in transplants, affecting up to 23% of cadaver transplants and 6% of living transplants [112]. The delay may last from days to weeks and may require temporary dialysis. Complete nonfunction by definition does not resolve and requires a return to dialysis.

## RENAL OSTEODYSTROPHY

Osteodystrophy has long been recognized as a complication of renal disease, and bone disease can affect patients with even mild kidney disease [5]. Renal osteodystrophy is defined as an alteration of bone morphology in patients with CKD, and it is considered one component of CKD-mineral and bone disorder. The causes of renal osteodystrophy are multifactorial. It may be the result of disorders associated with high bone turnover, such as osteitis fibrosa (caused by high PTH levels), or disorders caused by low turnover, such as osteomalacia due to aluminum accumulation. In patients with long-term advanced renal disease, amyloid disease can also develop.

Clinical symptoms of osteodystrophy may be absent until advanced biochemical changes have occurred. Although lesions progress throughout the disease course, symptoms and/or signs generally do not occur until the patient is already on maintenance dialysis. When present, symptoms include pain and stiffness and may present the same as arthritis.

As noted, one of the major causes of osteodystrophy associated with CKD is increased PTH levels. Increased PTH levels may be the result of phosphorous retention, decreased calcitriol levels, alteration in parathyroid growth and function, decreased serum calcium levels, or skeletal resistance to PTH [5]. Phosphorous retention (due to decreased elimination of phosphorous) has been shown to cause decreased ionized calcium levels. This causes the parathyroid glands to increase secretion of PTH, which causes the kidneys to decrease phosphorous absorption in the proximal tubules. The result is a normalization of phosphorous levels but an abnormal increase in PTH levels. Studies have shown that high phosphorous levels in vitro directly stimulate PTH secretion [5].

Phosphorous retention alone, however, cannot explain the high levels of PTH seen in early renal disease. During early renal disease, elevated PTH levels may be present in patients who have normal phosphate levels. Furthermore, studies have shown that hypocalcemia is not a cause of the increased PTH levels seen in these patients [5; 113]. While the exact mechanism of decreased calcitriol levels in renal disease may in fact be due to a combination of many factors, including high phosphorous levels and decreased renal mass (resulting in decreased production of calcitriol), it is becoming clearer that supplementation with calcitriol may help prevent renal osteodystrophy.

Despite the fact that control of phosphorous and calcium levels will not entirely prevent osteodystrophy, management of these levels is still important. As renal disease progresses, the kidneys lose their ability to properly eliminate phosphorous. Increased serum phosphorous can then lead to decreased calcium levels. To correct hypocalcemia and/or hyperphosphatemia, supplemental calcium is often given. Calcium between meals is more readily absorbed than supplementation with meals. When given with meals, calcium binds with phosphorous and leads to its elimination in the gastrointestinal tract. The use of stomach acid-lowering medications (such as proton pump inhibitors) can also lead to problems in calcium absorption. Increased phosphate levels not associated with decreased calcium levels can be treated with non-calcium phosphorous binders [5].

## USE OF CONTRAST MEDIUM IN PATIENTS WITH RENAL DISEASE

The use of radiocontrast media is becoming increasingly common in the United States. Unfortunately, contrast dye is nephrotoxic and exposes patients to the risk of AKI. It is estimated that cardiac catheterizations alone are responsible for 120,000 cases of contrast-induced AKI annually [114]. The overall incidence of contrast-induced nephropathy (CIN) is 5% to 38%, depending on the presence of risk factors [114].

CIN is defined as an increase in baseline serum creatinine of at least 0.5 mg/dL or a rise of more than 25% from baseline within one to five days after administration of contrast medium [114; 115]. Contrast dye nephropathy is the third leading cause of hospital-acquired acute renal failure [115]. Risk factors include pre-existing renal disease (i.e., serum creatinine greater than 1.4 mg/dL or eGFR less than 60 mL/min/1.73 $m^2$), age older than 75 years, diabetic nephropathy, sepsis, CHF, and hypovolemia [115; 116].

Strategies that may or may not help prevent CIN have been identified. Prevention is the cornerstone of CIN management, and hydration therapy is the foundation of CIN prevention [115]. Research indicates that furosemide and mannitol do not decrease the incidence of CIN and in fact may increase the rate by dehydrating patients [117]. Studies involving the prophylactic administration of high-dose *N*-acetylcysteine (NAC) have produced mixed results, possibly due to differences in dosages and hydration protocols. KDIGO guidelines recommend the use of oral NAC in conjunction with hydration for patients at increased risk of CIN [7]. In one study, patients received NAC twice daily for two days beginning on the day before the procedure [118]. To prevent one case of contrast-induced acute renal failure, the number needed to be treated with NAC was 8. The traditional dose is 600 mg twice daily, but more recent research has shown benefit from 1,200 mg twice daily [115; 116].

The use of sodium bicarbonate infusion pre- and postexposure to contrast medium has also been shown to help prevent the incidence of CIN. In a 2004 study, 119 patients were randomized to receive either sodium bicarbonate or sodium chloride at a rate of 3 mL/kg for one hour prior to their procedure followed by 1 mL/kg for six hours post-procedure [119]. The study was ultimately halted early due to a lower rate of acute renal failure in the sodium bicarbonate group, and remaining patients all received sodium bicarbonate. Follow-up analysis showed that 8.4 patients needed to be treated with sodium bicarbonate to prevent one case of CIN [119]. Absolute data from the study showed that 13.6% of patients in the sodium chloride group developed acute contrast-induced nephropathy; in the bicarbonate infusion group, only 1.7% of patients developed acute contrast nephropathy [119]. A 2018 randomized, placebo-controlled trial assessed the efficacy of intravenous NAC for prevention of CIN following diagnostic and/or interventional procedures requiring administration of contrast medium [120]. A total of 222 patients were randomly assigned to receive either NAC or placebo. All patients received IV hydration with normal saline before and after catheterization. CIN occurred in 30 of the 222 patients (13.5%), including 9 of 108 (8.3%) in the NAC group and 21 of 114 patients (18.4%) in the control group. Elevated serum creatinine 10 to 15 days after administration of the contrast medium was associated with an increased risk of adverse events [120]. A retrospective cohort study conducted at the Mayo Clinic assessed the risk of CIN with the use of sodium bicarbonate, NAC, or a combination of the two [121]. Compared with no treatment, sodium bicarbonate alone was associated with an increased risk of CIN, while NAC alone or in combination with sodium bicarbonate did not significantly affect the incidence of CIN [121]. Other therapies being investigated for the prevention of CIN include the use of vitamins C and E and prostaglandin E1 (PGE1), but additional research is needed [122; 123].

In addition to CIN, another threat to patients with renal disease undergoing administration of contrast medium is nephrogenic systemic fibrosis. As discussed, nephrogenic systemic fibrosis occurs almost exclusively in patients with advanced renal disease who receive gadolinium-based contrast dye. First identified in 1997 in California, this disease is systemic, can involve all major organs, and is potentially fatal. The exact mechanism by which gadolinium-based contrast causes nephrogenic systemic fibrosis is poorly understood. Patients can develop the disease at any time postexposure (including after several years), with most patients developing symptoms two to eight weeks after exposure [124].

The symptoms of nephrogenic systemic fibrosis are varied but include skin symptoms (e.g., tightening, hardening, swelling, raised red patches, burning, itching), skeletomuscular symptoms (e.g., muscle weakness and contractures, bone pain), and ocular symptoms (e.g., yellow spots on the conjunctiva).

Patients typically first present with distal extremity swelling followed by skin changes. While nephrogenic systemic fibrosis may not occur for years following exposure, after it develops patients may describe a progression of symptoms that occurs over days to months, with 5% of patients experiencing a rapid course [124; 125]. On clinical exam, the skin may appear "woody" or have an "orange peel" texture. As gadolinium is frequently used in MRI or magnetic resonance angiogram (MRA) procedures, the patient may have a history of one of these procedures and having received an intravenous medication at the time of the study. Biopsy is necessary to confirm diagnosis.

Treatment for nephrogenic systemic fibrosis is only symptom based, and there is no known cure. Extracorporeal photopheresis (ECP) seems to be the best treatment modality for nephrogenic systemic fibrosis; however, its effects are mild and the treatment is expensive [126]. Guidelines have vastly decreased the number of cases of nephrogenic systemic fibrosis by limiting the dose of gadolinium-based contrast agents; rapidly dialyzing patients following administration of gadolinium-based contrast agents; delaying gadolinium-based contrast agents in acute renal failure until renal function improves or dialysis is started; and avoiding use of nonionic linear agents in patients with renal failure, particularly when proinflammatory conditions are coincident [127; 128; 129; 130]. However, there is no way of definitively preventing nephrogenic systemic fibrosis when administering gadolinium-based contrast medium to renal failure patients; postexposure dialysis does not appear to decrease the risk. Therefore, the FDA has issued several warnings regarding its administration to patients with renal disease [84]. In 2010, a "black box" warning was added to the insert for gadolinium-based contrast that states clinicians should screen all patients for kidney disease prior to administration of the agents [84]. Most gadolinium-based products should not be used in patients with AKI or severe CKD, including gadopentetate dimeglumine (Magnevist), gadodiamide (Omniscan), and gadoversetamide (OptiMARK). Clinicians should refer to manufacturers' instructions and FDA warnings prior to the use of gadolinium in all patients, especially those with known renal disease or patients with risk factors for acute and/or chronic kidney disease.

## HIV AND RENAL FAILURE

While most clinicians do not generally think of renal failure as a consequence of HIV, in fact nephropathy is the most common form of renal disease in HIV-positive individuals [131]. Kidney disease is a fairly common complication of HIV disease, ranging from nephropathy to kidney injury due to antiretroviral therapy and prerenal AKI due to dehydration [131].

### ACUTE KIDNEY INJURY

Prior to the advent of highly active antiretroviral therapy (HAART), the incidence of AKI in HIV-positive individuals was fairly high, affecting up to 20% of hospitalized patients [131]. After the introduction of HAART, the incidence of AKI in hospitalized patients has fallen to approximately 3%, which is still about twice that of non-HIV-positive hospitalized individuals [131; 132]. The causes of AKI in hospitalized patients are quite heterogeneous, including hypovolemia, acute tubular necrosis, hemolytic uremic syndrome, and drug-induced AKI and HIV-associated nephropathy [131].

### CHRONIC KIDNEY INJURY

The incidence of CKD among patients with HIV infection varies widely based on the population sampled and on the definition of CKD used [132]. Furthermore, some studies have used the presence of proteinuria as a marker of disease (due to the ease of measurement) rather than NKF guidelines [132]. Epidemiologic studies place the rate of kidney disease in HIV-infected populations in the United States at approximately 7% to 8%, with microalbuminuria present in as many as approximately 30% of patients [131].

In other areas of the world, CKD in HIV-infected patients is not well documented and the rate varies based on definitions and methods of sampling. For instance, screening studies defining persistent proteinuria as an indicator of CKD revealed prevalence rates of 27% in India, 12.3% in Iran, and 5.6% in Brazil [132]. In Africa, the prevalence of HIV-associated renal disease is widely variable at 38% in Nigeria, 33.5% in Zambia, 20% in Uganda, and 5.5% to 6% in South Africa [132]. Rates are always found to be higher than those in noninfected populations [131].

## HIV-ASSOCIATED NEPHROPATHY

The prevalence of asymptomatic HIV-associated nephropathy may be much higher than statistics suggest, as HIV-associated nephropathy is only diagnosed by kidney biopsy [131]. Individuals with HIV comprise an estimated 1.5% of the United States ESRD population, and the prevalence of ESRD in this population continues to rise [132]. It has also been found to disproportionately affect minority patients. A study of 2 million U.S. veterans found that HIV conferred the same risk of ESRD among black patients as diabetes, but no such increased risk of ESRD was found among white patients with HIV [133]. HIV-associated nephropathy as a cause of ESRD affects almost exclusively persons of African descent, who account for approximately 90% of cases [132].

### Clinical Presentation

HIV-associated nephropathy generally presents as proteinuria in a setting of progressive HIV disease (including increasing viral load and decreased CD4 count) accompanied by rapidly decreasing renal function [132]. This classic presentation, as well as accumulated research, has led experts to believe that HIV-associated nephropathy is a direct result of HIV infection of the kidneys. In fact, HIV RNA helicase A has been found in the kidneys of patients with undetectable viral loads, leading some to believe that the kidneys may be a reservoir for HIV [131].

### Diagnostic Studies

The work-up of patients suspected of having HIV-associated nephropathy should focus on eliminating other causes of kidney disease, especially hepatitis C. Also, the possibility of drug-related kidney injury should be thoroughly investigated [132]. The HAART drug tenofovir is known to cause AKI and should be stopped immediately if a patient is found at any point to have impaired renal function. As noted, an absolute diagnosis of HIV-associated nephropathy requires kidney biopsy, which will reveal specific changes [132].

### Treatment

The primary goal of treatment of HIV-associated nephropathy is to prevent or limit the progression of the HIV infection. A diagnosis of HIV-associated nephropathy is an indication for the use of HAART, regardless of viral load [134]. Because proteinuria is present in HIV-associated nephropathy, the use of ACE inhibitors may be beneficial, and their use has been shown to decrease the incidence of ESRD in patients with HIV-associated nephropathy [131; 132; 135].

In general, the treatment of renal disease and ESRD in HIV-infected populations should follow the same standards as those noninfected patients with renal disease. The same standards of care for anemia, dialysis, transplantation, and prevention of CAD should be followed. Of particular importance is following guidelines for dosage adjustment of medications [132]. Most HIV drugs require adjustment in renal failure, and clinicians should follow manufacturers' recommendations.

EVIDENCE-BASED PRACTICE RECOMMENDATION

The Infectious Diseases Society of America recommends that HIV-infected patients with kidney disease be referred to a nephrologist for diagnostic evaluation when there is a clinically significant decline in GFR that fails to resolve after potential nephrotoxic drugs are removed, there is albuminuria in excess of 300 mg per day, hematuria is combined with either albuminuria/proteinuria or increasing blood pressure, or for advanced CKD management.

(https://academic.oup.com/cid/article/59/9/e96/422813. Last accessed November 21, 2024.)

**Strength of Recommendation/Level of Evidence:** Strong/low

### *Hemodialysis*

While the presence of HIV infection calls for rigorous adherence of Universal Precautions, special techniques are not required for hemodialysis. In fact, Standard Precautions are used for all patients on hemodialysis regardless of infection status. The dialysate should be regarded as potentially infectious body fluid, although no transmissions have been linked to dialysate to date [136]. Because of the increased susceptibility to infections, peritoneal dialysis is not widely advocated for this patient population [132].

### *Kidney Transplantation*

With the widespread use of HAART, studies have shown that patients with HIV do well after transplantation [134]. Concerns that immunosuppression would accelerate the progression of HIV disease have not been supported. HIV-positive individuals with stable disease pretransplant and no prior opportunistic infections have been found to continue to have stable disease post-transplant [132]. However, patients with HIV experience high rates of acute allograft rejection [132]. Guidelines generally call for adult transplant candidates to have a CD4 count greater than 300 cells/$mm^3$ and an undetectable viral load [109; 132]. Guidelines vary by center and differ for children, who generally should be transplanted as soon as possible to avoid developmental delays [131].

It is important for clinicians not to regard HIV disease as a terminal illness. The advent of HAART has transformed HIV into a chronic disease, and patients with HIV may live for decades with appropriate treatment [137]. Like many chronic illnesses, renal function may be affected and should be managed in accordance with established guidelines.

## HEPATITIS C AND RENAL DISEASE

Chronic hepatitis C infection is independently associated with the development of CKD [138; 139]. A meta-analysis published in 2015 demonstrated that chronic hepatitis C infection was associated with a 51% increase in the risk of proteinuria and a 43% increase in the incidence of CKD [139]. There is also a higher risk of progression to ESRD in persons with chronic hepatitis C infection and CKD, and an increased risk of all-cause mortality in persons on dialysis [140; 141]. Hepatitis C can directly cause renal disease via membranoproliferative glomerulonephritis and cryoglobulinemia [142; 143]. Patients on hemodialysis are at increased risk of infection via contaminated dialysis equipment or transfusion-related infection. Because patients with hepatitis C and renal disease tend to suffer from severe liver disease, these patients should have a liver biopsy (unless contraindicated) to check for fibrosis and cirrhosis.

After biopsy, a decision should be made on whether to pursue treatment for hepatitis C. Standard therapy consists of interferon and ribavirin. However, ribavirin is cleared by the kidneys and is contraindicated in patients with a GFR <50 mL/min/1.73 $m^2$ [29]. Close monitoring of hemoglobin levels and high-dose erythropoietin are needed to prevent severe anemia during the treatment period [144]. Several studies are investigating the use of ribavirin in patients with hepatitis C and ESRD, and guidelines may change [145; 146].

It is important to discuss treatment options with patients who may later be considered for transplantation. Cirrhosis is a contraindication to renal transplantation alone, but patients with cirrhosis may be evaluated for a combination renal and liver transplantation. Patients who can be treated prior to transplantation should be, as post-transplant treatment carries risk of rejection. Also, immunosuppression may lead to high viral loads in untreated patients. Consultation with a gastroenterologist specializing in liver disease should be obtained.

## RENAL DISEASE AND PREGNANCY

Renal disease can be a pre-existing condition or a consequence of pregnancy. Certain types of renal disease (e.g., pre-eclampsia) are unique to pregnancy, while other types, such as CKD associated with hypertension, reduce fertility and can have serious adverse effects on pregnancy and fetal and maternal outcomes [147; 148].

### RENAL CHANGES DURING PREGNANCY

In even a typical, uncomplicated pregnancy, renal dynamics are affected. Renal plasma flow increases dramatically, and by the second trimester, GFRs can reach 150% of normal [147; 148]. Accordingly, BUN and serum creatinine normally decrease. Blood pressure should fall in the first 24 weeks by approximately 10 mm Hg and return to normal levels by term [147]. Glucosuria also occurs in normal pregnancy due to changes in tubular function and decreased serum sodium levels (by approximately 5 mEq/L). Overall kidney size increases by approximately 1–1.5 cm, and the ureters dilate. This, coupled with changes in the pelvis, can lead to urinary stasis and an increase in urinary tract infections. Proteinuria up to 300 mg/day may occur even in normal pregnancy [147; 148].

### RENAL DISEASE SECONDARY TO PREGNANCY

Renal disease associated with pregnancy can take many forms. Perhaps the most common is prerenal azotemia associated with hyperemesis gravidarum. Treatment of this condition usually only requires replacement of fluids via intravenous administration. Acute tubular necrosis can occur with severe dehydration as well as secondary to shock or sepsis (or septic abortion). Treatment can require fluids, antibiotics, and if severe, dialysis [147].

Pre-eclampsia is a syndrome of proteinuria and hypertension that affects up to 5% of all pregnancies, while eclampsia is the occurrence of seizures in a patient with pre-eclampsia [147]. Pre-eclampsia does not usually develop until after the 32nd week of pregnancy, but it may develop much earlier in patients with CKD or hypertension. Risks factors include prepregnancy hypertension, diabetes, and CKD. Management of pre-eclampsia begins with bed rest but can include use of antihypertensives. Methyldopa, labetalol, and hydralazine are generally used, although this indication is off label. ACE inhibitors are contraindicated in pregnancy and can cause fetal loss, and diuretics are usually avoided in euvolemic patients. Intravenous magnesium sulfate can be used to prevent seizures. After 32 weeks' gestation, worsening pre-eclampsia warrants early delivery; eclampsia always mandates immediate delivery [147; 148].

### PREGNANCY AND CKD

In pregnant women, CKD can affect both the outcome of the pregnancy and the long-term outcome of the underlying renal disease. While fertility is decreased in CKD, pregnancy can occur, even in patients on dialysis. Outcomes vary considerably with degree of disease. Women with stable systemic lupus erythematosus (SLE), asymptomatic autosomal dominant polycystic kidney disease, or mild CKD and no hypertension may expect to have fairly normal outcomes [147].

Effects of pregnancy on CKD include deterioration of renal function. If this occurs quickly in early pregnancy, with no apparent diagnosis, renal biopsy should be considered [147]. In patients with mild CKD, renal function may be entirely preserved. Studies have shown that only 16% of pregnant patients with mild CKD and a baseline serum creatinine less than 1.5 mg/dL experienced a decline in renal function and only 6% of this subgroup progressed postpartum to ESRD [149]. Of patients with moderate CKD (serum creatinine: 1.5–2.4 mg/dL), one study found that 20% developed ESRD [150]. So, outcomes vary widely but are fairly predictable based on prepregnancy level of renal function [147].

## PREGNANCY AND LUPUS

SLE is frequently seen in women of childbearing age and is a common cause of renal disease in pregnancy. Approximately half of all SLE patients will experience a flare of their disease while pregnant, and in some cases, this manifests as lupus nephritis [147]. Lupus nephritis is characterized by proteinuria, hypertension, and decreased GFR. This constellation of symptoms may make lupus nephritis difficult to differentiate from pre-eclampsia, but a biochemical work-up for markers of lupus is helpful in making the distinction. Treatment of SLE flares in pregnancy is difficult due to the teratogenic nature of most SLE drugs, and up to 50% of all of these pregnancies result in fetal loss [147; 148].

## DIALYSIS

While ESRD results in decreased fertility, 1% to 7% of all women on dialysis who are of childbearing age will become pregnant [151]. Successful pregnancies have been documented, especially since 1980, but outcomes are still grim; only 25% to 50% of pregnancies result in live births [151]. Many pregnancies result in spontaneous abortion in the second trimester, and 85% of surviving infants are born premature. Outcomes for pregnancies that continue are good, with a fetal survival rate as high as 71% [147]. Maternal complications include severe worsening of hypertension and even death. It should be noted that the diagnosis of pregnancy cannot be made based on the usual measure of human chorionic gonadotropin (hCG), as beta-hCG is elevated in patients on dialysis [147; 148]. Ultrasound is generally necessary for confirmation of suspected pregnancy.

## PREGNANCY AFTER TRANSPLANTATION

Since 1958, more than 5,000 women have given birth post-transplant [152]. Women who previously were unable to conceive while undergoing dialysis often have a return of fertility after transplant, and up to 12% of all women of childbearing age may become pregnant [151]. Outcomes are generally quite good, with up to a 90% fetal survival rate [148]. Patients should be counseled that a properly planned and monitored pregnancy is possible, including preconception counseling by the transplant team. Recommendations for patients considering pregnancy include changing immunosuppressive regimens to limit dosages of prednisone and azathioprine and stopping mycophenolate mofetil and sirolimus six weeks prior to conception. Ideally, the patient should be two years post-transplant and in good health, with a serum creatinine level less than 2.0 mg/dL. There should be no recent or ongoing rejection, and patients should be normotensive and have minimal or no proteinuria [147; 148].

Even patients with optimal prepregnancy planning and good health can expect to experience some complications. The need to take immunosuppressive agents raises the maternal risk for hypertension and the fetal risk for size smaller than gestational age. Pre-eclampsia occurs in one-third of all transplant patients, and 50% of pregnancies require preterm delivery secondary to hypertension. Finally, there is an increased risk of opportunistic infections such as cytomegalovirus, herpes, and toxoplasmosis [147].

## MENTAL HEALTH AND RENAL DISEASE

Chronic kidney disease, like many chronic illnesses, places burdens on both patients and families. Even patients without pre-existing mental health problems can experience depression, stress, anxiety, and mental status changes caused by uremia. The burden is even greater for patients who have pre-existing mental health issues prior to diagnosis. Clinicians treating patients with CKD should be aware of the need to screen patients for mental health issues as well as the challenges in treating patients given the limitations in prescribing.

Depression can precede renal disease (as is the case with many chronic illnesses), evolve with it (perhaps worsened by the systemic effects of renal disease), or develop after a diagnosis has been made. A diagnosis of major depression need not wait until the patient sees a psychiatrist, as this may greatly lengthen the time to treatment. Patients should be routinely screened starting with initial presentation using standard screening tools such as the Hamilton Rating Scale for Depression (HAM-D). Screening tools may be administered by any competent, trained member of the interdisciplinary treatment team, including nurses and social workers. Abnormal results should trigger a more in-depth assessment or referral. Major areas of assessment should include risk for suicide, homicide, or harm to others; need for inpatient treatment; previous history of mental illness; previous treatment of mental illness; assessment of social support and resources; and patient preferences for treatment and attitudes regarding mental illness.

Treatment of nonsuicidal patients who are found to be appropriate for outpatient care usually begins with a selective serotonin reuptake inhibitor. These medications are preferred in renal disease due to their relatively benign side effect profile and their lack of renal clearance resulting in no need to modify dosage.

The combination of bipolar disorder and renal disease can be challenging to both patients and clinicians. Many medications used in the treatment of bipolar disorder can be either directly contraindicated in renal disease (e.g., lithium) or can worsen diseases that cause renal disease (e.g., atypical antipsychotics). Clinicians should work closely to develop a plan of care that controls the patient bipolar disorder without worsening their renal functioning.

Schizophrenia has been associated with an increased relative risk of development of type 2 diabetes, the leading cause of renal disease in the United States. While newer atypical antipsychotics have a decreased risk of extrapyramidal symptoms, the incidence of weight gain and diabetes is higher than in patients taking older generation antipsychotics [153; 154]. Schizophrenia is associated with impaired perception of reality, notably delusions and hallucinations, and these patients may not believe the diagnosis of renal disease, especially when the disease is asymptomatic.

## PATIENT AND FAMILY EDUCATION

Patient education in renal failure is highly complex. CKD and ESRD require carefully coordinated care. Enrollment in diabetes classes (when appropriate), renal diet cooking classes, and support groups can be of tremendous benefit. By gradually introducing different educational materials and enabling the patient to help control the course of the disease, healthcare providers can help restore a sense of independence and confidence in the patient.

### PROVIDING INFORMATION

It is crucial for healthcare professionals to realize that chronic illness is often a new and unanticipated event to the patient and family. Therefore, concrete information is vital. At the initial diagnosis, the family may be overwhelmed and struggling to come to terms with the illness. They may also be grappling

to understand new medical jargon and trying to assimilate a tremendous amount of information in order to make decisions about medical care plans. At this juncture, enhancing communication between the primary physician or nephrology team and the patient/family is the primary goal [155]. Technical information about the illness, prognosis, and care regimen should be conveyed. Healthcare professionals should be sensitive to the fact that this information may need to be relayed on several occasions. During this time, a list of resources and referrals may be helpful [155].

It is beneficial for caregivers and family members to understand normal changes that are part of human development and the life cycle, changes that are specifically related to the illness, or possibly an interaction of both [156]. Social isolation may occur. Therefore, it becomes a complicated issue to determine whether a particular behavioral change is the result of normal human development or illness-related.

Technical information related to the daily care of the patient should also be relayed. Family members may have to be taught how to lift and move patients without hurting themselves or the patient and how to administer medications or dialysis [156]. Family members should be reminded and educated about the physical consequences of the illness. Patients, for example, may experience fatigue as a result of the medications and/or the illness; however, some family members may become frustrated with the patient and interpret the patient as being lazy and taking advantage of the sick role [156]. Healthcare professionals should be fully knowledgeable about resources on both the local and national level to assist families in coordinating care for both the patient and themselves. Resources and services include places to access special equipment, legal and financial information, respite care, counseling, and support groups [156].

## EXPLORING THE MEANING OF CHRONIC ILLNESS AND AMBIGUOUS LOSS

The emphasis is to provide an opportunity for patients and family members to explore their feelings of loss, sorrow, mourning, and grief. Interventions also focus on helping to cope with or accept loss of physical functioning and capabilities [157].

Chronic illness can be the source of ambiguous loss, which is defined as loss without the finality of death but also with no certainty that the person will return to his or her previous level of functioning [158]. The goal is not necessarily to eliminate this sense of loss, but rather to increase family tolerance and coping. After identifying the loss, the family would work collaboratively to make decisions regarding day-to-day care and activities. Depression, which is commonly experienced among caregivers, may also be viewed as symptomatic of ambiguous loss. Therefore, practitioners can help encourage caregivers to not assume all the burden of responsibility, but rather to delegate and distribute the work. This may mean obtaining respite assistance [158].

One of the more difficult tasks is for patients and family members to understand and make sense of the ambiguous loss [158]. They can begin by looking at their own family's socialization, spiritual and religious values, and perspective (e.g., viewing the world optimistically).

## SELF-CARE FOR FAMILY MEMBERS

In order to prevent burnout, family members and caregivers should learn to take care of themselves. Caregivers often experience a host of conflicting emotions, including guilt, sadness, anxiety, and exhaustion. They often feel that they should not express negative feelings, believing that it will adversely affect the patient [156]. Healthcare professionals should routinely ask caregivers how they are feeling and coping, and then validate their experiences and feelings.

Caregivers should also be encouraged to obtain respite care. Respite refers to any type of service, either informal or formal, that offers relief and assistance for family members to cope with the challenges of chronic illness [159]. Informal respite assistance may include extended family members, neighbors, and friends who might periodically help with meal preparations, transportation, or housekeeping.

## FAMILY THERAPY

Family therapy can be a useful intervention to assist families in acknowledging and accepting the patient's illness as well as the treatment plan and prognosis [155]. It can help families develop coping skills to manage the challenges of the continual stressors related to chronic illness and identify maladaptive family patterns, such as enmeshment, triangulation, overprotectiveness, and rigidity [155]. In addition, role expectations can be clarified among family members, and lines of communication can be opened, and at times, restored, if certain family members feel overloaded with caregiving responsibilities [156].

## PSYCHOEDUCATIONAL GROUPS

Psychoeducational groups were first used in families with members who had schizophrenia; however, they have been adapted for use with other clinical populations. Psychoeducational groups typically involve a didactic and support component, whereby family members convene for 10 to 12 structured sessions on a biweekly basis [160]. The didactic component focuses on both cognitive information and behavioral change. Caregivers, for example, listen to a series of mini-lectures that focus on disease etiology, treatment, and management [160]. Problem-solving skills and coping strategies are often discussed. Caregivers are encouraged to use these newly-learned skills and apply them at home. The support component of the psychoeducational groups provides a forum for family members to talk about various issues that may come up in the caregiving situation. Facilitators and other family members provide validation and recognition of feelings.

## SUPPORT GROUPS/SELF-HELP GROUPS

Support and self-help groups are facilitated either by volunteers or healthcare professionals. They may vary, but will provide information regarding the illness and disease process, symptom management, emotional support around caregiving, advocacy, or a combination of these services [156]. Several support groups exist for patients, and more information about specific online or in-person groups is available from the American Association of Kidney Patients, the Renal Support Network, and the Kidney and Urology Foundation of America (***Resources***).

## CONSIDERATIONS FOR NON-ENGLISH-PROFICIENT AND IMMIGRANT PATIENTS/FAMILIES

Provisions for patients with limited English language proficiency are required under federal law, and the Department of Health and Human Services and the Office of Civil Rights view a lack of adequate interpretation as discrimination, based on the Civil Rights Act of 1964 [161]. Additionally, adhering to guidelines for working with patients with limited English proficiency helps to foster a beneficial working relationship and improved patient outcomes.

According to U.S. Census Bureau data from 2022, more than 67.8 million Americans speak a language other than English in the home, with more than 25.7 million of them (8.2% of the population) reporting that they speak English less than "very well" [162]. Clinicians should ask their patients what language is spoken at home and what language they prefer for their medical care information, as some patients prefer their native language even though they have said they can understand and discuss medical information in English [163].

When the healthcare professional and the patient speak different languages, a professional interpreter should be used. Studies have demonstrated that the use of professional interpreters rather than "ad hoc" interpreters (untrained staff members, family members, friends) facilitates a broader understanding and leads to better outcomes [161; 164; 165].

Using a family member as a translator confuses the role of that member in the family, may involve confidentiality issues, and may lead to a modified message to protect the patient. In addition, individuals with limited English language skills have indicated a preference for professional interpreters rather than family members [166]. Professional interpreters have recommended that clinicians can further enhance the quality of care by meeting with interpreters before discussions of bad news and by explicitly discussing with the interpreter whether strict interpretation or cultural brokering is expected [167].

The practitioner should always address the patient directly. For example, the practitioner should query the patient, "How do you feel?" versus asking the interpreter, "How does she feel?" The practitioner should also always refer to the patient as "Mr./Mrs. D," rather than "he" or "she." This avoids objectifying the patient. In addition, at the start of the session, the practitioner should clearly identify his/her role and the interpreter's role [168]. This will prevent the patient from developing a primary relationship or alliance with the interpreter, turning to the interpreter as the one who sets the intervention [169]. The practitioner also should be attuned to the age, gender, class, and/or ethnic differences between the patient and the interpreter [168]. For example, if the patient is an older Asian male immigrant, and the interpreter is a young, Asian female, the practitioner must be sensitive to whether the patient is uncomfortable, given the fact he may be more accustomed to patriarchal authority structures. At the conclusion of the session, it is advisable to have a debriefing time between the practitioner and the interpreter to review the session [168; 169; 170].

On the patients' side, they may be wary about utilizing interpreters for a host of reasons. They may find it difficult to express themselves through an interpreter [168]. If an interpreter is from the same community as the patient, the patient may have concerns about sharing private information with an individual who is known in the community and the extent to which the information disclosed would remain confidential. In some cases, raising the issue of obtaining an interpreter causes the patient to feel insulted that their language proficiency has been questioned. Finally, if an interpreter is from a conflicting ethnic group, the patient may refuse having interpreter services. The ideal situation is to have a well-trained interpreter who is familiar with health and mental health concepts.

Immigrant patients with renal failure may feel unable to return to their home countries, due to a lack of available dialysis and proper specialty care in their home countries. Changes in healthcare law restricting federal funding to legal residents may cause significant problems for hospital-based dialysis centers providing lifesaving care for patients who have no means of reimbursement and no medical services waiting for them in their home countries.

## END-OF-LIFE CARE

An end-of-life discussion is recommended in the presence of stage 4 or 5 CKD or ESRD [171; 172; 173]. Hospice is generally approved when patients with ESRD are not candidates for dialysis, have a creatinine clearance less than 15 mL/minute, and/or have a serum creatinine level greater than 8 mg/dL (or 6 mg/dL in patients with diabetes) [174]. Guidelines from the Renal Physicians Association note that prognosis should be fully discussed with all patients who have stage 4 or 5 disease or ESRD [172]. Clinicians should carefully prepare for the discussion of prognosis by reviewing the patient's medical record and talking to other healthcare professionals involved in the care of the patient [175]. Because there is variation among patients with regard to their desire for information, clinicians should follow the "ask-tell-ask" approach: ask the patient if he or she is willing to discuss prognosis; if yes, discuss the prognosis and then ask the patient to confirm his or her understanding [171; 176]. When discussing prognosis, quantitative estimates are more understandable for patients and family than qualitative ones (e.g., "poor"), and general timeframes for survival should be given [171; 176; 177; 178]. In addition, clinicians should emphasize that prognosis is determined by looking at large groups of patients and that it is harder to predict survival for an individual [171; 172]. The discussion of prognosis is often not documented in the patient's record, but it should be [175].

Clinical guidelines have begun to address the use of aggressive treatment at the end of life. The Renal Physicians Association recommends forgoing dialysis for patients with CKD or ESRD who have "very poor prognosis" [172]. Early discussion of preferences for life-sustaining measures is especially important. Nearly three-quarters of people will be unable to participate in some or all of the decisions about their care at the end of life [179]. Documentation of preferences helps inform decision making by the physician and the patient's healthcare proxy (surrogate decision maker). Clinicians should encourage their patients to designate a healthcare proxy early in the course of a life-limiting disease [171; 180; 181]. Patients should be urged to clarify their wishes with their chosen proxy, as a proxy often inaccurately predicts a patient's wishes or may have values that conflict with those of the patient [179].

## CASE STUDIES

### CASE STUDY 1

Patient A is a white man, 55 years of age, with diabetes. His HbA1c is 11%, and he suffers from diabetic retinopathy. Upon presentation, his blood pressure is 147/88 mm Hg, cholesterol is 213 mg/dL, and LDL is 136 mg/dL. His serum creatinine is 1.3 mg/dL. He is 5 foot 10 inches tall, his weight is 223 pounds, and he suffers from peripheral neuropathy. Patient A reports not having seen a primary care provider in years and is not on medication. He works at a factory and does not have health insurance.

***Discussion**: A few points come to mind when reviewing Patient A's history. Patients with poorly controlled diabetes are at an increased risk of renal disease. For every point the HbA1c is above normal, the incidence of end organ damage rises 10%. In this patient, the presence of end organ damage (i.e., retinopathy and neuropathy) indicates a high probability of renal disease. It is important to remember serum creatinine does not rise substantially until late in the renal disease process.*

Patient A is found to have proteinuria on dipstick testing. A 24-hour urine collection reveals a GFR of 57 mL/min/1.73 $m^2$. This categorizes the patient as having stage 3 CKD with hypertension and diabetes.

Patient A's primary care physician discusses this diagnosis with him and they develop a management plan, including medication and diet to better control his diabetes, with an HbA1c goal of less than 7%. He is also placed on an ACE inhibitor and a statin to achieve a blood pressure less than 130/85 mm Hg and an LDL less than 70 mg/dL. Because the patient has no health insurance, generic formulations of simvastatin (for hyperlipidemia) and lisinopril (for hypertension) are prescribed. The patient also starts generic metformin 1 g twice daily.

***Discussion**: According to the NKF guideline, the goals of treatment should be to diagnose and treat the specific causes of CKD, reduce the risks of cardiovascular disease, slow progression, and evaluate and treat complications and comorbidities.*

*When given to patients with advanced renal disease, metformin can lead to lactic acidosis, which can be fatal. Therefore, it should not be prescribed to men with serum creatinine levels of 1.5 mg/dL or greater or to women with serum creatinine levels of 1.4 mg/dL or greater. Patient A's serum creatinine will be regularly monitored; if the level rises to greater than 1.5 mg/dL, the metformin must be halted due to the risk of lactic acidosis.*

*Goals for HbA1c, LDL, and blood pressure should be secondary prevention goals for patients with diabetes and CKD. The target LDL is <70 mg/dL, and blood pressure should be less than 130/85 mm Hg. The HbA1c goal for patients with diabetes should be within 10% of normal, taking into account that studies have shown that older patients with cardiovascular disease actually have worse outcomes with HbA1c levels less than 6%.*

*Use of less expensive generic medications can greatly increase compliance, especially for uninsured patients. So, this was a good choice for Patient A. The costs associated with tests should also be considered. Although Medicare prefers reimbursing for "bundled" labs (e.g., chem-7 or chem-20), very often a single test, such as a serum creatinine, may be less expensive than a bundled panel of tests. The HbA1c is a test that changes slowly over the course of 90 days (the average lifespan of a red blood cell) and does not require more frequent monitoring. After the LDL goal has been reached, monitoring cholesterol less frequently may be considered as well.*

## CASE STUDY 2

Patient B is a white woman, 35 years of age, with a history of frequent urinary tract infections who now presents with gross hematuria. On physical exam, she is thin with a palpably enlarged right kidney. On questioning, she states that her mother had some sort of "cyst disease" of the kidney. She further states that her mother died of a heart attack several years ago, at 62 years of age. A renal ultrasound reveals numerous large, fluid-filled cysts on the right kidney and several cysts on the left kidney. Further imaging also reveals a fluid-filled cyst visible on the liver. A consultation with nephrology and a geneticist results in a diagnosis of autosomal dominant polycystic kidney disease (ADPKD).

***Discussion**: ADPKD is the fourth leading cause and the leading genetic cause of ESRD, and the most common life-threatening hereditary disease in the United States. ADPKD occurs in approximately one of every 1,000 live births. Children of affected individuals have a 50% chance of inheriting the disorder.*

*Patients with ADPKD can present with flank pain, hematuria, and/or palpable kidneys. Individuals with a family history are considered to have ADPKD if ultrasound reveals two unilateral or bilateral cysts in patients 15 to 30 years of age, two or more cysts in each kidney for patients 30 to 59 years of age, or four or more cysts in each kidney in patients older than 60 years of age. For patients with no known genetic risks (either from family history or genetic testing), the diagnostic criteria are three or more unilateral or bilateral cysts in patients 15 to 39 years of age or two or more cysts in each kidney for patients 30 to 59 years of age.*

*While the predominant clinical feature of ADPKD is renal disease (50% of affected patients have ESRD by 60 years of age), extrarenal manifestations are also common, which suggests that the disease may involve a generalized collagen disorder. As well as liver and pancreatic cysts, patients have an increased risk of cerebral hemorrhage due to intracranial aneurysms, cardiac valve abnormalities, aortic root dilation, and abdominal hernias.*

## CASE STUDY 3

Patient C is a black woman, 53 years of age, who is currently employed as an administrative assistant at a Veterans' Hospital. She has a long history of bipolar disorder and has been stable for many years on a combination of lithium and olanzapine. She states that in the last several years her weight has increased from 155 pounds to 217 pounds; her height is 5 feet 4 inches. She complains of frequent thirst and urination, lethargy, weakness, and blurred vision. A medical work-up reveals the following:

- Fasting blood glucose: 210 mg/dL
- HbA1c: 9.4%
- BUN: 83 mg/dL
- Serum creatinine: 3.4 mg/dL
- iPTH: 83 pg/mL
- TSH: 17 mIu/L
- Serum cholesterol: 230 mg/dL
- LDL: 163 mg/dL
- Blood pressure: 164/93 mm Hg

***Discussion**: Many widely prescribed medications for bipolar disorder have a variety of serious long-term side effects. Olanzapine has a documented risk of weight gain, hyperglycemia, type 2 diabetes, and in rare cases, diabetic ketoacidosis. The FDA requires a "black box" warning in the medication packaging warning of these side effects. While widely used for many years, lithium also has both endocrine and renal side effects.*

Patient C is directed to report to her local emergency room, where she receives intravenous fluids for dehydration, insulin, amlodipine for hypertension, and glyburide for diabetes. Her primary care practitioner starts her on levothyroxine for hypothyroidism and simvastatin for high cholesterol. She is also referred to endocrinology and nephrology. Her psychiatrist will conduct an evaluation of her psychiatric medications.

***Discussion***: *Collaboration between specialists and primary care providers is a necessary component to care of patients with renal disease. Many psychiatric medications can impact the care of patients with renal disease, worsen pre-existing diabetes and hypertension, or cause weight gain. Often, these side effects may be lessened by a change in medications. While psychiatric providers may be reluctant to change medications when a patient has been stabilized on his or her current regimen, patient safety may necessitate it. It is important that all team members be alert for signs and symptoms of psychiatric decompensation, especially if a patient is undergoing medication changes while simultaneously dealing with a new medical diagnosis.*

## CONCLUSION

Renal disease has reached epidemic proportions in the United States, and the management of this complicated condition presents a challenge to clinicians of all disciplines. Treating the millions of affected individuals requires enormous resources from an already overburdened system. Creativity, dedication, and passion will be required to find new and innovative solutions. Clearly, more must be done to prevent renal disease and improve patients' quality of life.

## RESOURCES

**American Association of Kidney Patients**
https://aakp.org

**American Kidney Fund**
https://www.kidneyfund.org

**American Society of Nephrology**
https://www.asn-online.org

**Dialysis Patient Citizens**
https://www.dialysispatients.org

**International Society for Hemodialysis**
http://www.ishd.org

**National Kidney Foundation**
https://www.kidney.org

**National Kidney Foundation**
**Disease Outcomes Quality Initiative**
https://www.kidney.org/professionals/kdoqi

**Renal Support Network**
https://www.rsnhope.org

**United Network for Organ Sharing**
https://unos.org

**Implicit Bias in Health Care**

The role of implicit biases on healthcare outcomes has become a concern, as there is some evidence that implicit biases contribute to health disparities, professionals' attitudes toward and interactions with patients, quality of care, diagnoses, and treatment decisions. This may produce differences in help-seeking, diagnoses, and ultimately treatments and interventions. Implicit biases may also unwittingly produce professional behaviors, attitudes, and interactions that reduce patients' trust and comfort with their provider, leading to earlier termination of visits and/or reduced adherence and follow-up. Disadvantaged groups are marginalized in the healthcare system and vulnerable on multiple levels; health professionals' implicit biases can further exacerbate these existing disadvantages.

Interventions or strategies designed to reduce implicit bias may be categorized as change-based or control-based. Change-based interventions focus on reducing or changing cognitive associations underlying implicit biases. These interventions might include challenging stereotypes. Conversely, control-based interventions involve reducing the effects of the implicit bias on the individual's behaviors. These strategies include increasing awareness of biased thoughts and responses. The two types of interventions are not mutually exclusive and may be used synergistically.

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