

Nephrology

Edward F. Foote, Pharm.D., FCCP, BCPS

Wilkes University
Wilkes-Barre, Pennsylvania

Nephrology

Edward F. Foote, Pharm.D., FCCP, BCPS

Wilkes University
Wilkes-Barre, Pennsylvania

Learning Objectives

1. Identify a patient at risk of, or presenting with, acute kidney injury and formulate an appropriate recommendation.
2. Identify a patient at risk of, or presenting with, drug-induced kidney disease and formulate an appropriate recommendation.
3. Compare and contrast the available methods to assess kidney function. Using appropriate data, assess kidney function in a patient.
4. Formulate an evidence-based treatment plan for managing the most common medical problems in patients with chronic kidney disease (CKD), including anemia, CKD mineral and bone disorder, and renal osteodystrophy.
5. Construct a treatment plan to slow the progression of CKD in patients with hypertension and diabetes.
6. Describe the pharmacokinetic effects of peritoneal and hemodialysis on drug disposition.
7. List the most common nephrolithiasis prevention measures and treatment options.

Self-Assessment Questions

Answers and explanations to these questions can be found at the end of the chapter.

Questions 1–3 pertain to the following case.

B.T. is a 50-year-old woman with stage 5 CKD who has received hemodialysis (HD) for the past 7 years. Her medical history includes type 2 diabetes mellitus (DM), hypertension, and gastroesophageal reflux disease. B.T. regularly attends her HD sessions and stays for the full treatment. Medications include calcium carbonate two 500-mg (1000 mg total) tablets with meals and one tablet with snacks, insulin glargine 40 units every morning and insulin apart 3–6 units with meals, ranitidine 150 mg once daily, aspirin 81 mg once daily, renal multivitamin one tablet daily, and atorvastatin 20 mg once daily. She receives epoetin alfa 8000 units intravenously and paricalcitol 2 mcg intravenously at each dialysis session. B.T. has received dietary counseling, and she states that she adheres to her diet as closely as possible. Her serum albumin concentration is 4.0 g/dL. Laboratory values include intact parathyroid hormone (iPTH) 700 pg/mL, calcium 10.4 mg/dL, and phosphorus 6.8 mg/dL.

1. Which is the best recommendation with respect to controlling the phosphorus concentration in this patient?
 - A. Increase calcium carbonate to 1.5 g with meals and 1 g with snacks.
 - B. Discontinue calcium carbonate, and institute calcium acetate 1334 mg with meals and 667 mg with snacks.
 - C. Discontinue calcium carbonate, and institute aluminum hydroxide 1 g with meals and snacks.
 - D. Discontinue calcium carbonate, and institute sevelamer 800 mg with meals and snacks.
2. For this patient, the nephrology team is also considering the addition of cinacalcet to directly reduce the PTH concentration. Which laboratory value is most important to monitor for safety?
 - A. Liver function.
 - B. Calcium.
 - C. PTH.
 - D. Creatinine.

B.T.'s epoetin dose has been unchanged for 6 months. Most recently, her laboratory values were as follows: hemoglobin 8.8 g/dL, transferrin saturation (TSAT) 14%, and serum ferritin 90 ng/mL. In the past month, her hemoglobin concentration was 9.4 g/dL. There are no obvious signs of infection or bleeding.

3. Which therapeutic changes would be most appropriate to manage this patient's anemia?
 - A. Administer intravenous iron sucrose 100 mg with each dialysis session for 10 dialysis sessions.
 - B. Counsel the patient to take ferrous sulfate twice daily with meals.
 - C. Initiate folic acid 1 mg orally once daily.
 - D. Increase the epoetin dose to 10,000 units intravenously with each HD session.

4. Which drug is most likely to be removed by high-flux HD?

Drug	Water Solubility	Molecular Weight, Da	Volume of Distribution, L/kg
A	Moderate	180	1
B	High	1400	7
C	High	250	0.3
D	Low	300	2

- A. Drug A.
B. Drug B.
C. Drug C.
D. Drug D.
5. An adult patient with stage 5 CKD who is receiving maintenance automated peritoneal dialysis (PD) is experiencing abdominal pain, fever, and cloudy dialysate bags. The nephrology team suspects peritonitis and wants to initiate empiric antibiotic therapy. Which is the best empiric antibiotic therapy for this patient?
- A. Oral ciprofloxacin and metronidazole.
B. Intraperitoneal vancomycin.
C. Intravenous gentamicin alone.
D. Intraperitoneal cefazolin and ceftazidime.

Questions 6 and 7 pertain to the following case.

T.R. is a 54-year-old African American man who presents with diagnosed type 2 DM. His serum creatinine concentration (SCr) is 1.6 mg/dL, and a spot albumin/creatinine ratio (ACR) is 410. His blood pressure (BP) is 145/89 mm Hg.

6. Which would provide the best therapeutic intervention at this time to slow diabetic kidney disease progression?
- A. Metformin.
B. Lisinopril.
C. Metoprolol.
D. Amlodipine.

7. Which dietary intervention is best to reduce albuminuria in patients such as T.R.?

- A. Protein-restricted diet.
B. Omega-3 fatty acid administration.
C. Low-carbohydrate (Atkins) diet.
D. Low-potassium diet.

8. A 76-year-old woman presents with an acute febrile illness that includes some diarrhea and generalized aches. She has been taking ibuprofen for pain for the past 48 hours and presents to the emergency department feeling “awful.” Her laboratory tests and physical examination suggest she is not volume depleted. Her SCr has doubled since her past visit 1 year ago. Her physician believes she has acute kidney injury (AKI). A urinalysis does not reveal red blood cells (RBCs) or white blood cells (WBCs) or cellular casts. Which is the most likely diagnosis in this case?

- A. Prerenal AKI.
B. Hemodynamically mediated AKI.
C. Intrinsic AKI.
D. Postrenal AKI.

I. ACUTE KIDNEY INJURY OR ACUTE RENAL FAILURE

A. Definitions and Background

1. An AKI is defined as an acute decrease in kidney function or glomerular filtration rate (GFR) over a period of hours, days, or even weeks and is associated with an accumulation of waste products and (usually) volume.
 - a. Definitions vary. A commonly used definition is an increase in SCr of 0.5 mg/dL or greater **OR** a decrease of 25% or greater in the GFR of patients with previously normal kidney function **OR** an increase of 1 mg/dL or greater in SCr in patients with CKD. It is also defined according to urine output (less than 0.5 mL/kg/hour for at least 6 hours).
 - b. The Acute Kidney Injury Network (AKIN): Diagnostic criteria require **one** of the following within a 48-hour period: An absolute increase in SCr of more than 0.3 mg/dL **OR** a 50% or greater increase in baseline SCr **OR** urine output less than 0.5 mL/kg/hour for more than 6 hours. In 2012, Kidney Disease: Improving Global Outcomes (KDIGO) published guidelines that concurred with the AKIN definition.
2. Community-acquired AKI
 - a. Low incidence (0.02%) in otherwise healthy patients
 - b. As high as 13% incidence among patients with CKD
 - c. Usually has a very high survival rate (70%–95%)
 - d. Single insult to the kidney, often drug induced
 - e. Often reversible but may contribute to faster decline in function in patients with CKD
3. Hospital-acquired AKI
 - a. Has a moderate incidence (2%–5%) and moderate survival rate (30%–50%)
 - b. Single or multifocal insults to the kidney
 - c. Can still be reversible
 - d. Intensive care unit–acquired AKI: From 5% to 6% of patients in intensive care develop AKI during unit stay, and patients who develop this condition in the intensive care unit have a low survival rate (10%–30%).

B. Risk Factors Associated with AKI

1. Preexisting CKD (estimated glomerular filtration rate [eGFR] less than 60 mL/minute/1.73 m²)
2. Volume depletion (e.g., vomiting, diarrhea, poor fluid intake, fever, diuretic use)
3. Effective (intravascular) volume depletion (e.g., congestive heart failure [CHF], liver disease with ascites).
4. Use of nephrotoxic agents/medications: Intravenous radiographic contrast, aminoglycosides, amphotericin, nonsteroidal anti-inflammatory drugs (NSAIDs) and cyclooxygenase-2 (COX-2) inhibitors, angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs), cyclosporine, and tacrolimus
5. Obstruction of the urinary tract

C. Classifications of AKI

1. Prerenal AKI
 - a. Initially, the kidney is undamaged.
 - b. Characterized by hypoperfusion to the kidney
 - i. Systemic hypoperfusion: Hemorrhage, volume depletion, drugs, CHF
 - ii. Isolated kidney hypoperfusion: Renal artery stenosis, emboli
 - c. Urinalysis will initially be normal (no sediment) but concentrated.
 - d. Physical examination: Hypotension, volume depletion
2. Functional (also called *hemodynamically mediated*) AKI—Often seen in ambulatory care

-
- a. Similar to prerenal AKI, kidney is undamaged.
 - b. Caused by reduced glomerular hydrostatic pressure
 - c. Most often medication related (cyclosporine, ACEIs and ARBs, and NSAIDs)
 - d. Patients present with a concentrated urine and elevated SCr. Note that small increases (<30%) in SCr are acceptable.
3. Intrinsic AKI
 - a. Kidney is damaged, and damage can be linked to structure involved: Small blood vessels, glomeruli, renal tubules, and interstitium.
 - b. Most common cause is acute tubular necrosis (ATN); other causes include acute interstitial nephritis, vasculitis, and acute glomerulonephritis.
 - c. Urinalysis will reflect damage; urine is generally not concentrated.
 - d. Physical examination: Normotensive, euvoletic, or hypervolemic depending on the cause. Check for signs of allergic reactions or embolic phenomenon.
 - e. History: Identifiable insult, drug use, infections
 4. Postrenal AKI
 - a. Kidney is initially undamaged. Bladder outlet obstruction is the most common cause of postrenal AKI. Lower urinary tract obstruction may be caused by calculi. Ureteric obstructions may be caused by clots or intraluminal obstructions. Extrarenal compression can also cause postrenal disease. Increased intraluminal pressure upstream of the obstruction will result in damage if obstruction is not relieved.
 - b. Urinalysis may be nonspecific.
 - c. Physical examination: Distended bladder, enlarged prostate
 - d. History: Trauma, benign prostatic hypertrophy, cancers
- D. Prevention of AKI
1. Avoid nephrotoxic drugs when possible.
 2. Ensure adequate hydration unless otherwise contraindicated (e.g., CHF, liver cirrhosis).
 3. Patient education
 4. Drug therapies to decrease incidence of contrast-induced nephropathy—See Drug-Induced Kidney Damage section.
- E. Treatment and Management of Established AKI
1. Prerenal azotemia: Correct primary hemodynamics.
 - a. Normal saline if volume depleted
 - b. Pressure management if needed
 - c. Blood products if needed
 2. Functional AKI—Remove offending agent.
 3. Intrinsic: No specific therapy universally effective
 - a. Eliminate the causative hemodynamic abnormality or toxin.
 - b. Avoid additional insults.
 - c. Fluid and electrolyte management to prevent volume depletion or overload and electrolyte imbalances
 - d. Nutrition support is important, but no specific recommendations are widely accepted.
 - e. Medical therapy: Vasculitis may be treated on an outpatient basis.
 4. Postrenal AKI: Relieve obstruction. Early diagnosis is important. Consult urology and/or radiology.

II. DRUG-INDUCED KIDNEY DAMAGE

A. Introduction

1. Drugs are responsible for kidney damage through many mechanisms. Kidney damage can occur in both outpatient and inpatient settings. Evaluate potential drug-induced nephropathy on the basis of the period of ingestion, patient risk factors, and the propensity of the suspected agent to cause kidney damage.
2. Common risk factors
 - a. History of CKD
 - b. Increased age
 - c. Other nephrotoxins

B. Hemodynamically Mediated (Functional) AKI

1. Caused by an abrupt decrease in intraglomerular pressure through the vasoconstriction of afferent arterioles or the vasodilation of efferent arterioles
2. ACEIs and ARBs
 - a. Pathogenesis: Caused by vasodilation of the efferent arteriole. This leads to a decrease in glomerular hydrostatic pressure and a resultant decrease in GFR.
 - b. Presentation: Note that a relatively small increase in SCr (less than 30%) is normal. Elevation usually occurs within 2–5 days and stabilizes within 2–3 weeks. Usually reversible on drug discontinuation
 - c. Risk factors: Patients with bilateral (unilateral with a solitary kidney) renal artery stenosis, decreased effective kidney blood flow (CHF, cirrhosis), preexisting kidney disease, and volume depletion
 - d. Prevention: Initiate therapy with low doses of short-acting agents and gradually titrate. Switch to long-acting agents once tolerance is established. Initially, monitor kidney function and SCr often: Daily for inpatients, weekly for outpatients. Avoid use of concomitant diuretics, if possible, during therapy initiation.
 - e. Treatment: Discontinue agent.
3. Nonsteroidal anti-inflammatory drugs
 - a. Pathogenesis: Vasodilatory prostaglandins help maintain glomerular hydrostatic pressure by afferent arteriolar dilation, especially in times of decreased kidney blood flow. Administering an NSAID in the setting of decreased kidney perfusion reduces this compensatory mechanism by decreasing the production of prostaglandins, resulting in afferent vasoconstriction and reduced glomerular blood flow.
 - b. Presentation: Can occur within days of starting therapy. Patients generally have low urine volume and low urine sodium concentration. In addition, there are increases in blood urea nitrogen (BUN), SCr, potassium, edema, and weight.
 - c. Risk factors: Preexisting kidney disease, systemic lupus erythematosus, high plasma renin activity (e.g., CHF, hepatic disease), diuretic therapy, atherosclerotic disease, and advanced age
 - d. Prevention: Use therapies other than NSAIDs when appropriate (e.g., acetaminophen for osteoarthritis). Sulindac is a potent NSAID that may affect prostaglandin synthesis in the kidney to a lesser extent than other NSAIDs.
 - e. Treatment: If NSAID-induced AKI is suspected, discontinue drug and provide supportive care. Recovery is usually rapid.

-
4. Cyclosporine and tacrolimus
 - a. Pathogenesis: Causes vasoconstriction of afferent arterioles through possible increased activity of various vasoconstrictors (thromboxane A₂, endothelin, sympathetic nervous system) or decreased activity of vasodilators (nitric oxide, prostacyclin). Increased vasoconstriction from angiotensin II may also contribute.
 - b. Presentation: Can occur within days of starting therapy. Patients often present with hypertension, hyperkalemia, and hypomagnesemia. A biopsy is often needed for kidney transplant patients to distinguish drug-induced nephrotoxicity from acute allograft rejection.
 - c. Risk factors for toxicity: Increased age, high initial cyclosporine dose, kidney graft rejection, hypotension, infection, and concomitant nephrotoxins
 - d. Prevention
 - i. Monitor serum cyclosporine and tacrolimus concentrations closely.
 - ii. Use lower doses in combination with other non-nephrotoxic immunosuppressants.
 - iii. Calcium channel blockers may help antagonize the vasoconstrictor effects of cyclosporine by dilating afferent arterioles.
 - e. Treatment: Lower dose and/or discontinue agent.
- C. Intrinsic AKI
1. ATN: Most common drug-induced kidney disease in the inpatient setting
 - a. Aminoglycoside nephrotoxicity
 - b. Radiographic contrast media nephrotoxicity related to intravenous contrast use. Prevention: Mainstay is hydration. Acetylcysteine is widely used and may be initiated on an outpatient basis. Other medications have been tried, but there are no well-documented outcomes.
 - c. Cisplatin and carboplatin nephrotoxicity
 - d. Amphotericin B nephrotoxicity
 2. Tubulointerstitial disease
 - a. Involves the renal tubules and the surrounding interstitium
 - b. Onset can be acute or chronic. Acute onset generally involves interstitial inflammatory cell infiltrates, rapid loss of kidney function, and systemic symptoms (i.e., fever and rash). Chronic onset shows interstitial fibrosis, slow decline in kidney function, and no systemic symptoms.
 - c. Acute allergic interstitial nephritis
 - i. Cause of up to 3% of all AKI cases. Caused by an allergic hypersensitivity reaction that affects the interstitium of the kidney
 - ii. Many medications and medication classes can cause this type of kidney failure. The most commonly implicated are the β -lactams and the NSAIDs (although the presentations are different).
 - (a) Penicillins: Classic presentation of acute allergic interstitial nephritis. Signs/symptoms occur about 1–2 weeks after therapy initiation and include fever, maculopapular rash, eosinophilia, pyuria, hematuria, and proteinuria. Eosinophiluria may also be present.
 - (b) NSAIDs: Onset, much more delayed, typically begins about 6 months into therapy. Usually occurs in elderly patients receiving chronic NSAID therapy. Patients usually do not have systemic symptoms.
 - iii. Kidney biopsy may be needed to confirm diagnosis.
 - iv. Treatment includes discontinuing the offending agent and possibly initiating steroid therapy.
-

-
- D. Chronic Interstitial Nephritis
1. Lithium
 - a. Lithium: Develops insidiously over a period of years. Associated with elevated SCr, polydipsia, polyuria. Major risk factor is duration of therapy. Prevent by maintaining lithium concentrations as low as possible and avoiding dehydration. Symptoms may resolve with discontinuation.
 - b. Cyclosporine: Presents later in therapy (about 6–12 months) than hemodynamically mediated toxicity. Progressive and often irreversible
 2. Papillary necrosis
 - a. Form of chronic interstitial nephritis affecting the papillae, causing necrosis of the collecting ducts. Associated with diabetes, sickle cell disease, and other conditions but most commonly associated with analgesic use
 - b. Results from the long-term use of analgesics
 - i. “Classic” example was with products that contained phenacetin.
 - ii. Occurs more often with combination products
 - iii. Products containing caffeine may also pose an increased risk.
 - c. Evolves slowly as time progresses
 - d. Affects women more often than men
 - e. Difficult to diagnose, and much controversy remains regarding risk, prevention, and cause
- E. Postrenal (Obstructive) Nephropathy
1. Results from obstruction of urine flow after glomerular filtration
 2. Renal tubular obstruction
 - a. Caused by intratubular precipitation of tissue degradation products (uric acid, drug-induced rhabdomyolysis) or precipitation of drugs or their metabolites (sulfonamides, methotrexate, acyclovir, ascorbic acid)
 - b. Prevention includes pretreatment hydration, maintenance of high urinary volume, and alkalinization of the urine.
 3. Nephrolithiasis
 - a. Usually does not affect GFR, so does not have the classic signs/symptoms of nephrotoxicity
 - b. Some medications contribute to the formation of kidney stones: Triamterene, sulfadiazine, indinavir, and ephedrine derivatives.
- F. Glomerular Disease
1. Proteinuria is the hallmark sign of glomerular disease and may occur with or without a decrease in GFR.
 2. A few distinct drugs can cause glomerular disease:
 - a. NSAIDs: Associated with acute allergic interstitial nephritis
 - b. Heroin: Can be caused by direct toxicity or toxicity from additives or infection from injection, and end-stage renal disease (ESRD) develops in most cases.
 - c. Parenteral gold: Results from immune complex formation along glomerular capillary loops

III. CKD – OVERVIEW

Patient Cases

1. A 55-year-old man presents with a history of hypertension and newly diagnosed type 2 DM. He reports no alcohol use but does smoke cigarettes (1 pack/day). His medications include hydrochlorothiazide and valsartan. At your pharmacy, his BP is 130/80 mm Hg. A 24-hour urine collection reveals 0.4 g of albumin. A recent SCr is 1.9 mg/dL. His eGFR is 50 mL/minute/1.73 m². Which is the best answer with respect to the staging of kidney disease?
 - A. Stage 2.
 - B. Stage 3.
 - C. Stage 4.
 - D. Stage 5.

2. A 72-year-old white woman (height 63 inches, weight 48 kg) (ideal body weight 52.4 kg) presents to the clinic. She is visibly small and frail. The SCr, unchanged from the past year, is 0.4 mg/dL. Which is the best method to assess kidney function in this patient?
 - A. Cockcroft-Gault.
 - B. Modification of Diet in Renal Disease (MDRD) (study).
 - C. Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI).
 - D. Twenty-four-hour urine collection for creatinine clearance (CrCl).

A. Epidemiology, Definition, and Staging

1. Prevalence: Difficult to assess, according to the National Health and Nutrition Examination Survey (1999–2004); 16.8% of adults (20 years or older) have CKD, and more than 500,000 have kidney failure treated with kidney dialysis or transplantation. The prevalence of ESRD in the United States is increasing, whereas the incidence is relatively flat; hence, growth in the ESRD population is mainly because of the longer life span of these patients.
2. Definition of CKD, according to the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI): Kidney damage for more than 3 months, as defined by structural or functional abnormality of the kidney, with or without decreased GFR, manifested by either pathologic abnormalities or markers of kidney damage, including abnormalities in the composition of blood or urine or abnormalities in imaging tests **OR** GFR less than 60 mL/minute/1.73 m² for 3 months, with or without kidney damage
3. Albuminuria: Marker of kidney damage suggesting increased glomerular permeability. Can be assessed by timed urine collection, dipsticks, or ACR in a spot urine sample (most common). Normal ACR is less than 10 mg/g.
4. Stages of CKD
 - a. KDOQI
 - Stage 1 – GFR of 90 mL/minute/1.73 m² or greater with persistent kidney damage
 - Stage 2 – GFR 60–90 mL/minute/1.73 m² with persistent kidney damage
 - Stage 3 – GFR 30–59 mL/minute/1.73 m²
 - Stage 4 – GFR 15–29 mL/minute/1.73 m²
 - Stage 5 – GFR less than 15 mL/minute/1.73 m² or treatment by dialysis (5D)

- b. KDIGO: The GFR (G-stages) follows the original CKD classification scheme with some modifications:
- G1 – GFR greater than 90 mL/minute per 1.73 m²
 - G2 – GFR 60–89 mL/minute per 1.73 m²
 - G3a – GFR 45–59 mL/minute per 1.73 m²
 - G3b – GFR 30–44 mL/minute per 1.73 m²
 - G4 – GFR 15–29 mL/minute per 1.73 m²
 - G5 – GFR less than 15 mL/minute per 1.73 m² or treatment by dialysis (5D if undergoing dialysis)
- c. Staging of albuminuria by ACR (KDIGO). The absolute number of ACR is equivalent to the albumin excretion rate.
- A1 – ACR less than 30 mg/g (less than 3.4 mg/mmol) (normal to high normal)
 - A2 – ACR 30–300 mg/g (3.4–34.0 mg/mmol) (high)
 - A3 – ACR greater than 300 mg/g (greater than 34.0 mg/mmol) (very high)
- B. Etiology
1. Diabetes (40% of new ESRD cases in the United States)
 2. Hypertension (25% of new cases)
 3. Glomerulonephritis (10%)
 4. Others—Urinary tract disease, polycystic kidney disease, lupus, analgesic nephropathy, unknown
- C. Risk Factors
1. Susceptibility (associated with an increased risk, but not proved to cause CKD): Advanced age, reduced kidney mass, low birth weight, racial/ethnic minority, family history, low income or education, systemic inflammation, and dyslipidemia; mostly unmodifiable
 2. Initiation (directly cause CKD): Diabetes, hypertension, autoimmune disease, polycystic kidney diseases, and drug toxicity; may be modifiable by drug therapy
 3. Progression (result in faster decline in kidney function): Hyperglycemia, elevated BP, proteinuria, and smoking; modifiable by drug therapy
- D. Assessment of Kidney Function
1. Serum creatinine
 - a. Derived from the metabolism of creatinine in skeletal muscle and from dietary meat intake
 - b. Creatinine is freely filtered at the glomerulus, making it a good marker for kidney function. However, creatinine also undergoes tubular secretion, so CrCl always overestimates GFR.
 - c. SCr varies inversely with kidney function, and small changes in SCr represent more significant alterations in kidney function in patients with higher baseline function (see Figure 1).

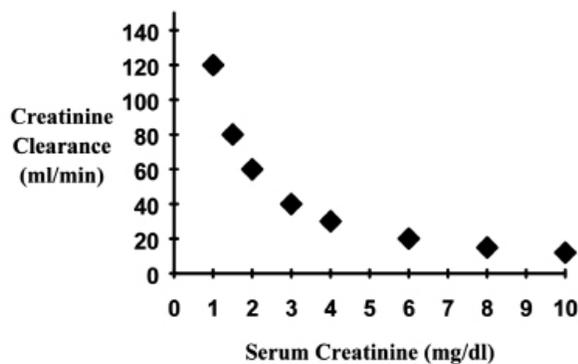


Figure 1. Relationship between serum creatinine concentrations and creatinine clearance.

- d. Concentration depends on age, sex, weight, diet, and muscle mass, so avoid use as the sole assessment of kidney function. Certain medications (cimetidine, trimethoprim) interfere with renal tubular secretion of creatinine and will raise SCr values without a change in GFR. Only clinically evident in patients with impaired kidney function
 - e. Most laboratories now use “standardized” cases of creatinine traceable to isotope dilution mass spectrometry, which will decrease the variability in results between laboratories. The MDRD and CKD-EPI equations have been adjusted.
2. Measurement of CrCl by 12- to 24-hour urine collection
 - a. Overestimates GFR by 10%–20% because of the tubular secretion of creatinine
 - b. Reserve for vegetarians, patients with low (or unusually high) muscle mass, patients with amputations, and patients needing dietary assessment, as well as when documenting need to start dialysis.
 - c. Urine collection will give a better estimate of CrCl in patients with very low muscle mass.
 - d. Limited use because of the logistics of collecting urine and blood samples
 3. Measurement of GFR: Insulin, iothalamate, and others. Not routinely used in clinical practice
 4. Estimated CrCl (eCrCl) using the Cockcroft-Gault equation:
$$[(140 - \text{Age}) \times \text{Actual Body Weight}] / [\text{SCr} \times 72] \times (0.85 \text{ if female})$$
 - a. Will overestimate kidney function in patients with low muscle mass. Do not “round up” low SCr values (opinion).
 - b. Some centers use ideal body weight in the equation (although original study used total body weight). For most patients the difference is not clinically meaningful.
 - c. Requires stable kidney function
 - d. Has not been revised by using the standardized creatinine assays, so use of this equation may result in a 10%–40% overestimation of CrCl
 - e. Commonly used for drug dosing
 5. Estimated GFR with MDRD study data equation
 - a. eGFR (mL/minute/1.73 m²) in patients with known CKD (GFR less than 60 mL/minute/1.73 m²)
 - b. Abbreviated MDRD considers age, SCr, sex, and race (African American) in estimation equation.
 - c. The abbreviated MDRD formula correlates well with the original MDRD formula and is simpler to use. The abbreviated equation and an adjusted equation for use with standardized creatinine are available at www.kidney.org/professionals/kdoqi/gfr_calculator.cfm.
 6. Estimated GFR with the CKD-EPI equation: Relatively new formula used to estimate GFR that is more accurate than MDRD for patients with an eGFR greater than 60 mL/minute/1.73 m². Available at www.kidney.org/professionals/kdoqi/gfr_calculator.cfm. This is the formula recommended by the National Kidney Foundation and is now being used by major laboratory testing companies.
 7. Equations incorporating cystatin C are available but not widely used. Compared to creatinine, production of cystatin C is much less influenced by a person’s age, sex, and size. May be particularly useful in patients with alterations in creatinine production (e.g., the elderly).
 8. For children, Schwartz and Counahan-Barratt formulas: Available at http://nephron.com/peds_nic.cgi
 9. For obese patients: With Cockcroft-Gault equation, use of total body weight will overestimate kidney function and the use of ideal body weight will underestimate it. There is no consensus on an adjusted body weight to use in these equations, but adding 20%–40% of excess weight to IBW has been suggested. Salazar-Corcoran equation was developed for use in obese patients and is superior to unadjusted Cockcroft-Gault equation but is not widely used.
 10. Pregnancy: Use of prepregnancy weight in one small study resulted in good estimates of CrCl. May wish to consider urine collection

IV. CKD – MANAGEMENT

Patient Case

3. A 60-year-old Asian American male patient with a history of hypertension and newly diagnosed type 2 DM comes to the clinic. He reports neither alcohol consumption nor smoking. His medications include atenolol 25 mg daily. At your pharmacy, his BP is 155/96 mm Hg and heart rate is 76 beats/minute. A 24-hour urine collection reveals 0.4 g of albumin. A recent SCr is 1.9 mg/dL. His eGFR is 37 mL/minute/1.73 m². Enalapril is added to this patient's regimen. Two weeks later, he presents back to his physician. His BP is 145/93 mm Hg. A repeated SCr measurement is 2.3 mg/dL, and his serum potassium is 5.2 mEq/L. Which is the best recommendation for this patient?
- Change enalapril to diltiazem (Cardizem CD). Monitor BP, SCr, and potassium concentration in 2 weeks.
 - Add chlorthalidone 50 mg daily. Monitor BP, SCr, and potassium concentration in 2 weeks.
 - Change enalapril to valsartan.
 - Increase atenolol.

A. General Management of CKD

- Treatment of reversible causes of renal failure
- Preventing or slowing the progression of renal disease
- Treatment of the complications of renal failure
- Adjusting drug dosages, when appropriate, for the eGFR level
- Identification and adequate preparation of the patient for whom renal replacement therapy will be required

B. Diabetic Nephropathy

- Pathogenesis
 - Hypertension (systemic and intraglomerular)
 - Glycosylation of glomerular proteins
 - Genetic links
- Diagnosis
 - Long history of diabetes
 - Proteinuria
 - Retinopathy (suggests microvascular disease)
- Monitoring
 - Type 1—Begin annual monitoring for microalbuminuria 5 years after diagnosis
 - Type 2—Begin annual monitoring for proteinuria immediately (do not know how long patients have had DM)
- Management/slowing progression—New KDOQI guidelines 2012 and KDIGO 2012
 - Aggressive BP management
 - In patients with diabetes and CKD with a urine albumin excretion of less than 30 mg/24 hours, the target BP is 140/90 mm Hg or less. If the urine albumin excretion is greater than 30 mg/24 hours, the goal BP is 130/80 mm Hg or less (KDIGO). The Eight Joint National Committee (JNC 8) recommends a BP goal of less than 140/90 mm Hg.
 - ACEIs and ARBs are preferred and should be used with an albuminuria of 30 mg/g or greater, even if the patient is normotensive.
 - Recommendation is to titrate to the maximal recommended dose (if tolerated).

- (b) Monitor serum creatinine and potassium values after 1 week for development of increased creatinine and hyperkalemia if using ACE inhibitors, ARBs, or diuretics.
 - (c) Hold ACEI/ARB if serum potassium concentration is greater than 5.6 mEq/L or if rises in SCr are greater than 30% after initiation.
 - iii. Most patients will also require a diuretic. (Thiazide with stages 1–3 and loop in stages 4–5.) If BP is greater than 160/100 mm Hg, start with two-drug regimen.
 - iv. Calcium channel blockers (non-dihydropyridine) are second line to ACEIs/ARBs for proteinuria.
 - v. According to JNC 8, ACEI and ARB combination is not recommended.
 - vi. Dietary sodium consumption should be less than 2.0 g daily. Modify DASH diet (Dietary Approaches to Stop Hypertension) to limit potassium intake as well.
 - vii. Spironolactone or eplerenone may reduce albuminuria but there is no meaningful clinical outcomes data.
 - viii. Aliskirin added to ARB may reduce proteinuria but data are limited and it is not recommended.
 - b. Blood glucose control: Glycosylated hemoglobin
 - i. About 7% for most patients
 - ii. Less than 7% not recommended for patients at risk of hypoglycemia
 - iii. Less aggressive with more advanced CKD/limited life expectancy/risk of hypoglycemia/comorbidities
 - c. Protein restriction: There may be a modest reduction in the decline of GFR in patients with CKD with a diet of 0.6–0.8 g/kg/day of protein. The American Diabetes Association does not recommend protein restriction. National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI) recommends target dietary protein intake of 0.8 g/kg/day, the recommended daily allowance, and avoidance of high-protein diets for patients with CKD stages 1-4.
- C. Nondiabetic Nephropathy
- 1. Manage hypertension.
 - a. If urine albumin excretion is less than 30 mg/24 hours, maintain a BP of 140/90 mm Hg or less. If urine albumin excretion is greater than 30 mg/24 hours, maintain a BP of 130/80 mm Hg or less.
 - b. If proteinuric and hypertensive, use an ACEI or an ARB. Often need to add (or start with) combination. Diuretic is usually the second drug. Monitor serum potassium concentration.
 - 2. Minimize protein in diet. Controversial. May slow progression according to MDRD study but may also impair nutrition. Very low protein diet may increase mortality.
- D. Other Guidelines to Slow Progression
- 1. Manage hyperlipidemia. There are conflicting data on the benefit of statin therapy solely for renal protection. However, statin therapy has shown cardiovascular prevention benefit in patients with CKD who are not yet receiving dialysis (Lancet 2011;377:2181-92). A reasonable goal is a low-density lipoprotein cholesterol concentration less than 100 mg/dL. Of note, do not institute statin therapy for patients with diabetes who are treated by dialysis because of the lack of a cardiovascular benefit (4D and AURORA trials) (KDOQI diabetes guidelines 2012). The 2013 American College of Cardiology/American Heart Association (ACC/AHA) Guideline on Blood Cholesterol do not recommend the routine use of statins for patients undergoing hemodialysis.
 - 2. Stop smoking.
 - 3. Avoid nephrotoxins especially NSAIDs.
 - 4. Maintain healthy diet, with moderate alcohol consumption.

V. COMPLICATIONS OF CKD**Patient Cases**

A 73-year-old man presents with an 8-year history of type 2 DM that has been treated with insulin. He presents with dyspnea on exertion and fatigue. His BP is 147/70 mm Hg. Fecal occult blood findings are negative. Medications include enalapril 10 mg daily, amlodipine 10 mg daily, rosuvastatin 10 mg daily, furosemide 40 mg daily, calcium acetate 667 mg three times daily with meals, and aspirin 81 mg daily. His BUN and SCr values are 75 mg/dL and 6.5 mg/dL, respectively. Six months ago, his SCr was 3.9 mg/dL. Other pertinent laboratory values include serum potassium 6.2 mEq/L, CO₂ 18 mEq/L, phosphorus 4.2 mg/dL, glucose 216 mg/dL, hemoglobin 8.9 g/dL, and eGFR 8 mL/minute/1.73 m². Serum ferritin is 259 ng/mL, serum iron 30 mcg/dL, and TSAT 28%.

4. Which is the most likely cause of anemia in this patient?
 - A. Absolute iron deficiency.
 - B. Dietary deficiency.
 - C. Epoetin (EPO) deficiency.
 - D. Enalapril.

5. The patient in Patient Case 4 starts intermittent HD therapy. One month later, you see him in the HD unit. He is tolerating HD well. His most recent hemoglobin measurement is 9.5 g/dL. His serum ferritin concentration is 70 ng/mL, and his TSAT is 12%. His BP is well controlled, and his other electrolytes are at goal. His medications are unchanged except that he now receives epoetin alfa 3000 units three times weekly with dialysis. What is the next, most appropriate step for this patient?
 - A. Add oral iron.
 - B. Add intravenous iron.
 - C. Increase the epoetin alfa dose.
 - D. Maintain therapy because the patient is at goal.

- A. Uremia: A Cluster of Symptoms Associated with CKD or AKI from any Cause. Symptoms are caused by the retention of nitrogenous waste products that are normally removed by the kidneys. Clinicians monitor BUN test results to assess uremic signs and symptoms (although urea is not likely the cause of uremic symptoms). Dialysis reduces the signs and symptoms of uremia by removing these waste products. Signs and symptoms of uremia include the following:
 1. Cardiovascular—Pericarditis, sodium and water retention, hyperlipidemia or dyslipidemia
 2. Gastrointestinal (GI)—Anorexia, taste changes, uremic fetor, constipation, nausea, and vomiting
 3. Blood—Anemia, impaired platelet function
 4. Skin—Dry skin, uremic pruritus, and uremic frost
 5. Restless legs syndrome, leg cramps
 6. Reduced reproductive function, erectile dysfunction
 7. Encephalopathy

- B. Anemia (updated KDIGO guidelines 2012)
 1. Several factors are responsible for anemia in CKD: Decreased EPO production (most important), iron deficiency (very common), shorter life span of RBCs, blood loss during dialysis, GI blood loss, anemia of chronic disease, and renal osteodystrophy.

2. Prevalence: Twenty-six percent of patients with a GFR greater than 60 mL/minute have anemia versus 75% of patients with a GFR less than 15 mL/minute.
3. Signs and symptoms—Similar to anemia associated with other causes. Anemia contributes to fatigue, cold intolerance, depression, reduced exercise capacity, dyspnea, and cardiac complications. Associated with increased morbidity and mortality, decreased quality of life, increased hospitalizations
4. Testing for anemia: For patients with CKD without anemia, measure hemoglobin concentrations when clinically indicated and at least annually in patients with CKD stage 3; twice yearly in patients with non-dialysis (ND) CKD stages 4–5; and at least every 3 months in patients with CKD stage 5 HD and CKD stage 5 PD. For patients with CKD and anemia not being treated with an erythropoiesis-stimulating agent (ESA), measure hemoglobin concentration when clinically indicated—At least every 3 months in patients with ND CKD stages 3–5 and at least monthly in patients with CKD stage 5 HD.
5. Diagnosis of anemia in adults and children older than 15 years who have CKD when the hemoglobin concentration is less than 13 g/dL in males and less than 12 g/dL in females
6. Anemia workup: For patients with anemia and CKD, include the following in the initial evaluation of anemia:
 - a. Complete blood cell count (CBC) to include hemoglobin, RBC indices, WBC counts with differential, and platelet count
 - b. Reticulocyte count
 - c. Serum ferritin (to measure stored iron)
 - d. Serum TSAT calculated as iron/total iron-binding capacity to measure available iron
 - e. Serum vitamin B₁₂ and folate
 - f. Stool guaiac to rule out GI bleed
7. Treatment—Treatment of anemia in CKD can decrease morbidity/mortality, reduce left ventricular hypertrophy, increase exercise tolerance, and increase quality of life. The CHOIR (Correction of Hemoglobin and Outcomes in Renal Insufficiency) trial enrolled ND-dependent CKD patients with GFR 15–50 ml/min/1.73 m². Study found that treatment to high hemoglobin concentrations (greater than 13 g/dL) increases cardiovascular events (N Engl J Med 2006;355:2085-98). More recently, the TREAT (Trial to Reduce Cardiovascular Events with Darbepoetin alpha Therapy) study failed to show a benefit in outcomes of death, CV event, or renal event but was associated with an increased risk of stroke in patients with ND CKD, diabetes, and moderate anemia (N Engl J Med 2009;361:2019-32).
 - a. Iron therapy
 - i. Most patients with CKD who are receiving EPO therapy require iron therapy to meet their needs (increased requirements, decreased oral absorption).
 - ii. Oral iron not recommended for patients with CKD who are undergoing HD; however, it can be used for patients with CKD who are undergoing PD and those not yet receiving dialysis.
 - iii. Administer intravenous iron in a patient with hemodialysis-dependent CKD and anemia (regardless of ESA use) if TSAT is 30% or less and ferritin concentration is 500 ng/mL or less. For patients with ND CKD, may consider a 1- to 3-month trial of oral iron. For pediatric patients, administer iron when TSAT is 20% or less and ferritin concentration is 100 ng/mL or less (KDIQO recommendations 2012).
 - iv. For adult patients with iron deficiency who are undergoing dialysis, an empiric cumulative or total dose of 1000 mg is usually given, and equations are rarely used. Maintenance therapy is often required. Dosing strategies vary but include weekly to monthly administration of intravenous iron.
 - v. Monitor TSAT and ferritin values as noted during EPO therapy.

- vi. Four commercial intravenous iron preparations have been approved in the United States (Table 1).
- vii. Monitor for 60 minutes post infusion for serious adverse reactions. Highest risk with dextran formulations
- viii. Avoid intravenous iron in patients with systemic infection (KDIGO 2012).

Table 1. Intravenous Iron Preparations Available in the United States

	Iron Dextran (Dexferrum and INFeD)	Ferric Gluconate (Ferrlecit, Nulecit)	Iron Sucrose (Venofer)	Ferumoxytol (Feraheme)
Replacement therapy TSAT	IVP: 100 mg IV three times weekly during HD for 10 doses (1 g) IVPB: 500–1000 mg in 250 mL of NSS infused for at least 1 hour (option for non-HD patients)	125 mg IV three times weekly during HD for eight doses (1 g)	100 mg IV three times weekly during HD for 10 doses (1 g) For non-dialysis CKD, 200 mg IV × five doses	510 mg at up to 30 mg/second, followed by a second 510 mg IV 3–8 days later (all CKD)
Iron overload TSAT	Hold therapy	Hold therapy	Hold therapy	Hold therapy
Initial test dose	Yes	No	No	No
Black box warning	Yes	No	No	No

CKD = chronic kidney disease; HD = hemodialysis; IV = intravenous(ly); IVP = IV push; IVPB = IV piggyback; NSS = normal saline solution; TSAT = transferrin saturation.

- b. Erythropoiesis-stimulating agents: (Note: ESAs are now under the U.S. Food and Drug Administration’s [FDA’s] Risk Evaluation and Mitigation Strategy [REMS] program.). Use REMS and modified dosing because of data showing increased risks of cardiovascular events with ESAs in patients with higher hemoglobin concentrations or at relatively rapid rises in hemoglobin concentration.
 - i. Epoetin alfa (Epoen, Procrit)
 - (a) Same molecular structure as human EPO (recombinant DNA technology)
 - (b) Binds to and activates EPO receptor
 - (c) Administered subcutaneously or intravenously
 - ii. Darbepoetin alfa (Aranesp)
 - (a) Molecular structure of human EPO has been modified from three *N*-linked carbohydrate chains to five *N*-linked carbohydrate chains; increased duration of activity
 - (b) The advantage is less frequent dosing (FDA approved every 1–2 weeks, has been used monthly off-label).
 - (c) Binds to and activates EPO receptor
 - (d) May be administered subcutaneously or intravenously. Conversion (epoetin to darbepoetin) recommendations are widely available.

- iii. Methoxy polyethylene glycol-epoetin beta (Mircera)
 - (a) Long-acting continuous erythropoietin receptor activator (CERA).
 - (b) Initially approved by the FDA in 2007 but had not been marketed due to patent infringement issues. Genentech recently entered into an exclusive distribution agreement with Fresenius Medical Care (FMC) Dialysis Company to distribute. FMC is the largest dialysis company in the U.S. so the use of this drug will be widespread.
 - (c) Same black box warnings as ESA's.
 - (d) Dosed every two weeks. Administered using pre-filled syringes.
- iv. Availability of biosimilar ESA's may be alternative to brand-name ESA's in the near future.
- c. KDIGO recommendations (2012) for ESAs
 - i. For adult patients with ND CKD and hemoglobin concentration of 10 g/dL or greater, suggest that ESA therapy not be initiated. The decision to initiate ESAs with hemoglobin concentration of less than 10 g/dL should be individualized, and benefits should be weighed against risk.
 - ii. For adult patients with CKD 5D, ESA therapy should be used to avoid hemoglobin concentrations of 9 g/dL by initiating an ESA when hemoglobin concentration is between 9 and 10 g/dL. The guidelines state that individualization is reasonable, and some patients may benefit from having ESAs initiated with hemoglobin concentration greater than 10 g/dL.
 - iii. Recommend that ESAs not be used to maintain hemoglobin concentration above 11.5 g/dL; individualized patients may benefit from hemoglobin concentration less than 11.5 g/dL. The ESA should not be used to intentionally increase hemoglobin concentrations above 13 g/dL.
- d. Modified dosing recommendations of ESAs from the FDA (June 2011): For patients with CKD, consider initiating ESA treatment when the hemoglobin concentration is less than 10 g/dL. This advice does not define how far below 10 g/dL the concentration should be for appropriate initiation of a patient's treatment. This advice also does not recommend that the goal be to achieve a hemoglobin concentration of 10 g/dL or a hemoglobin concentration above 10 g/dL. Individualize dosing, and use the lowest dose of ESAs that is sufficient to reduce the need for RBC transfusions; adjust dosing as appropriate. Because of more recent studies and updated labeling information, most units use a goal of 10–11 g/dL.
- e. ESA dose adjustment is based on hemoglobin response.
 - i. Adjustment variables are the same for epoetin alfa and darbepoetin alfa.
 - ii. Upward dosage adjustments should not be made more often than every 4 weeks. Downward adjustment, at any time
 - iii. In general, dose adjustments are made in 25% intervals (i.e., dosages adjusted upward or downward by 25% according to current dose).
- f. ESA monitoring
 - i. Monitor hemoglobin concentrations initially every 1–2 weeks and then every 2–4 weeks when stable.
 - ii. Iron stores should be monitored every 1–3 months.
 - iii. Monitor for adverse drug reactions such as hypertension (treat as necessary), pure red cell aplasia (rare), and allergic reactions.

Patient Case

6. A 60-year-old patient undergoing HD presents with a 10-year history of ESRD. His HD access is a left arteriovenous fistula. He has a history of hypertension, coronary artery disease, mild CHF, type 2 DM, and a seizure disorder. His medications are as follows: epoetin 14,000 units three times weekly at dialysis; a multivitamin (Nephrocaps) once daily; atorvastatin 20 mg daily; insulin; calcium acetate two tablets three times daily with meals; phenytoin 300 mg daily; and intravenous iron 100 mg monthly. Laboratory values are as follows: hemoglobin 10.2 g/dL; iPTH 800 pg/mL; sodium 140 mEq/L; potassium 4.9 mEq/L; SCr 7.0 mg/dL; calcium 9 mg/dL; albumin 2.5 g/dL; and phosphorus 7.8 mg/dL. Serum ferritin is 200 ng/mL, and TSAT is 32%. The patient's RBC indices are normal. His WBC count is normal. He is afebrile. What is most likely contributing to relative epoetin resistance in this patient?

- A. Iron deficiency.
- B. Hyperparathyroidism.
- C. Phenytoin therapy.
- D. Infection.

- g. Common causes of inadequate response to ESA therapy:
 - i. Before the widespread use of intravenous iron, iron deficiency was the most common cause of EPO resistance in patients undergoing dialysis. Iron deficiency is still quite common in patients with ND CKD.
 - ii. Infection and inflammation is a very common cause of EPO resistance, particularly in patients with CKD who are undergoing dialysis. Associated with elevated values of hepcidin, which inhibit iron absorption in the GI tract and reduce iron release from the reticuloendothelial system
 - iii. Other causes include chronic blood loss, renal bone disease/hyperparathyroidism, aluminum toxicity, folate or vitamin B₁₂ deficiency, inadequate dialysis, hospitalization, autoimmune disease, malignancies, malnutrition, hemolysis, and vitamin C deficiency. Medications that cause anemia in other patient populations should also be considered.

Patient Case

7. In addition to suggesting diet modifications and emphasizing adherence for the patient in Patient Case 6, which is the best approach to managing this patient's hyperparathyroidism and renal osteodystrophy?

- A. Increase calcium acetate.
- B. Change calcium acetate to sevelamer and add cinacalcet.
- C. Hold calcium acetate and add intravenous vitamin D analog.
- D. Add intravenous vitamin D analog.

Patient Case

8. A 45-year-old patient has hypertension, diabetes (diet controlled), and CKD (eGFR 40 mL/minute/1.73 m²). He receives maintenance therapy with atenolol, valsartan, and hydrochlorothiazide. He has no health insurance. His most recent laboratory values were within limits except for serum phosphorus, which, for the second month in a row, was 5.1 mg/dL. His serum calcium concentration is 9.4 mg/dL, and iPTH concentration is 40 pg/mL. He tells you that he is following a low-salt, low-potassium, and low-phosphate diet. Which is the most appropriate intervention at this point?
- A. Add calcium carbonate with meals.
 - B. Add calcium acetate with meals.
 - C. Add sevelamer with meals.
 - D. Add calcitriol.

C. Renal Osteodystrophy

1. Primary types of bone disease include osteitis fibrosa cystica (secondary hyperparathyroidism), adynamic bone disease (excessive suppression of parathyroid gland), osteomalacia (rare), and mixed disorder. Chronic kidney disease–mineral and bone disorder (CKD-MBD) is a newly described syndrome in which bone disease, mineral abnormalities, and extraskeletal calcification occur.
2. Pathophysiology of secondary hyperparathyroidism and osteitis fibrosa: High-turnover bone disease caused by secondary hyperparathyroidism. Calcium and phosphorus homeostasis is complex, involving the interplay of hormones affecting the bone, GI tract, kidneys, and PTH. Process may begin as early as when GFR is 60 mL/minute. The main abnormalities that contribute to hyperparathyroidism include the following:
 - a. Phosphate retention: May be the most important cause of hyperparathyroidism
Hyperphosphatemia caused by decreased renal excretion of phosphorus. Hyperphosphatemia induces hypocalcemia, decreases formation of activated vitamin D, and increases *PTH* gene expression.
 - b. Decreased free calcium concentrations
 - c. Decreased 1,25-dihydroxyvitamin D values
 - d. Reduced expression of vitamin D receptors and calcium-sensing receptors
 - e. Fibroblast growth factor-23 (FGF-23) elevation. FGF-23 reduces renal phosphate reabsorption and increases urinary phosphate excretion in healthy individuals, so values are increased in CKD because of hyperphosphatemia. Contributes to decreased vitamin D synthesis
3. Pathophysiology of adynamic bone disease is related to oversuppression of the parathyroid gland, most likely because of the excessive use of calcium-based phosphate binders and vitamin D products. In addition, diabetes and increasing age are risk factors.
4. Prevalence
 - a. Major cause of morbidity and mortality in patients undergoing dialysis
 - b. Very common. The incidence of adynamic bone disease is increasing.
5. Signs and symptoms
 - a. Insidious onset: Patients may experience fatigue and musculoskeletal and GI pain; calcification may be visible on radiography; bone pain and fractures can occur if progression is left untreated.
 - b. Laboratory abnormalities
 - i. Phosphorus
 - ii. Corrected calcium
 - iii. Intact parathyroid hormone

6. Treatment
 - a. Therapy goals
 - i. KDOQI (2003) (Table 2)

Table 2. KDOQI Guidelines for Ca, Phosphorus, Ca x PO₄ Product, and PTH in CKD Stages

	CKD Stage 3	CKD Stage 4	CKD Stage 5
Ca, mg/dL, ^a	Normal	Normal	8.4–9.5
Phosphorus, mg/dL	2.7–4.6	2.7–4.6	3.5–5.5
Ca × PO ₄ product	<55	<55	<55
PTH, pg/mL	35–70	70–110	150–300

^aUse the following: Corrected Calcium = Serum Calcium + (0.8 × [4.0 – Patient Albumin]).

Ca = calcium; CKD = chronic kidney disease; KDOQI = Kidney Disease Outcomes Quality Initiative; PO₄ = phosphate; PTH = parathyroid hormone.

- ii. KDIGO (2009)
 - (a) For patients with stage 3–5 CKD who are not yet undergoing dialysis, phosphate should be maintained in the normal range. Among dialysis patients receiving dialysis, phosphate should be lowered toward the normal range.
 - (b) The calcium concentrations in CKD 3–5, including for patients undergoing dialysis, should be maintained in the normal range.
 - (c) Although widely monitored in clinical practice and often used as an indication for non-calcium-based binders, KDIGO recommends that only the individual values for calcium and phosphorus, rather than the calcium x phosphorus product be monitored.
 - (d) The optimal PTH concentration in patients with ND CKD is unknown. In patients with CKD receiving dialysis, the PTH concentration should be maintained at 2–9 times the upper limit of normal for the particular PTH assay.
- b. Nondrug therapy
 - i. Dietary phosphorus restriction 800–1200 mg daily in stage 3 CKD or higher
 - ii. Dialysis removes various amounts of phosphorus, depending on treatment modalities, but, by itself, is insufficient to maintain phosphorus balances in most patients.
 - iii. Parathyroidectomy—Reserved for patients with unresponsive hyperparathyroidism
- c. Drug therapy
 - i. Phosphate binders: Take with meals to bind phosphorus in the gut; products from different groups may be used together for additive effect.
 - (a) Aluminum-containing phosphate binders (aluminum hydroxide, aluminum carbonate, and sucralfate): Effectively lower phosphorus concentrations. In general, avoid except for very short-term use (2–4 weeks) if serum phosphorus values are greater than 7 mg/dL (KDOQI guidelines). Not used as often because of aluminum toxicity (adynamic bone disease, encephalopathy, and EPO resistance)
 - (b) Calcium-containing phosphate binders (calcium carbonate and calcium acetate)
 - (1) Calcium carbonate is a widely used phosphate binder because of its low cost and efficacy.
 - (2) Calcium acetate: 667-mg capsule contains 167 mg of elemental calcium. Better binder than carbonate, so less calcium given. Unlike calcium carbonate, soluble with achlorhydria. Liquid formulation also available

-
- (3) Use of calcium salts may be limited by the development of hypercalcemia and overall positive calcium balance, which may increase the risk of vascular calcification and arterial disease. Particularly problematic when vitamin D analogs are used
 - (4) To prevent positive calcium balance, recommendations now limit total elemental calcium intake to 2000 mg daily (1500-mg binder; 500-mg diet).
- (c) Sevelamer: A nonabsorbable phosphate binder
- (1) Effectively binds phosphorus
 - (2) As with calcium, considered primary therapy in stage 5 CKD. In particular, consider if the calcium x phosphorus product is greater than 55 mg²/dL² (KDOQI) or if calcium intake exceeds the recommended dose with calcium-containing binders. Sevelamer use is also suggested for patients with corrected calcium concentration greater than 9.5 mg/dL.
 - (3) Decreases low-density lipoprotein cholesterol and increases high-density lipoprotein cholesterol
 - (4) Available as sevelamer hydrochloride (HCl) (Renagel tablet) and sevelamer carbonate (Renvela tablet and powder). Carbonate salt is the preferred agent because it provides a base load (carbonate). Worsening acidosis has been reported with the use of sevelamer HCl. May reduce absorption of quinolone antibiotics, levothyroxine and mycophenolate – Separate dosing.
- (d) Lanthanum carbonate (Fosrenol)
- (1) As effective as aluminum in phosphate-binding capability
 - (2) Tasteless, chewable/crushable tablet
 - (3) Indications basically the same as those for sevelamer
- (e) Sucroferric oxyhydroxide chewable tablets (Vephoro)
- (1) Iron-based (calcium-free)
 - (2) One tablet per meal as starting dose may be advantageous.
 - (3) Must be chewed (not swallowed whole). Can crush (disadvantage)
 - (4) Can cause black stools.
 - (5) Potential iron drug interactions with other orally administered drugs
- (f) General
- (1) A recent meta-analysis revealed a 22% decrease in all-cause mortality among patients randomly assigned to receive non–calcium-based binders versus calcium-based binders.
 - (2) Binders should be taken before meals. Between-meal calcium will result in more calcium absorption (which may be desired in some cases).
 - (3) Avoid calcium binders for patients who have both hyperphosphatemia and hypercalcemia because of the risk of calcification. In addition, avoid for patients with low PTH concentration (adynamic bone disease).
 - (4) May see calcium and sevelamer/lanthanum used in combination
 - (5) Intensive dialysis may also reduce phosphate values. This would include daily dialysis and nocturnal dialysis, both of which are relatively uncommon in the United States.

- ii. Vitamin D and vitamin D analogs: Suppress PTH synthesis and reduce PTH concentrations; therapy is limited by resultant hypercalcemia and hyperphosphatemia. Products include 25-hydroxyvitamin D (25-OH vitamin D) products (ergocalciferol and cholecalciferol) and 1,25-(OH)₂ vitamin D product and analogs (calcitriol, doxercalciferol, and paricalcitol).
- (a) Ergocalciferol: Recommended for CKD stages 3–5 in the presence of an elevated PTH concentration and documented vitamin D deficiency (25-hydroxyvitamin D concentration less than 30 ng/mL). Cholecalciferol has been used as well. Ergocalciferol is also being used for dialysis patients with a documented vitamin D deficiency, but there is no strong evidence to support this. Administration of ergocalciferol is probably safe.
 - (b) Calcitriol (Calcijex and Rocaltrol): The pharmacologically active form of 1,25-dihydroxyvitamin D₃ is FDA label approved for the management of hypocalcemia and the prevention and treatment of secondary hyperparathyroidism.
 - (1) Oral and parenteral formulations
 - (2) Does not require hepatic or renal activation
 - (3) Low-dose daily oral therapy reduces hypocalcemia but does not reduce PTH concentrations significantly.
 - (4) High incidence of hypercalcemia, limiting PTH suppression
 - (5) Dose adjustment at 4-week intervals
 - (c) Paricalcitol (Zemlar): Active vitamin D analog; FDA label approved for the treatment and prevention of secondary hyperparathyroidism
 - (1) Parenteral and oral formulations
 - (2) Does not require hepatic or renal activation
 - (3) Lower incidence of hypercalcemia than calcitriol (decreased mobilization of calcium from the bone and decreased absorption from the gut)
 - (d) Doxercalciferol (Hectorol): Vitamin D analog; FDA label approved for the treatment and prevention of secondary hyperparathyroidism
 - (1) Parenteral and oral formulations
 - (2) Prodrug, requires hepatic activation; may have more physiologic values
 - (3) Lower incidence of hypercalcemia than calcitriol (decreased mobilization of calcium from the bone and decreased absorption of calcium from the gut)
- iii. Calcimimetic agents (cinacalcet HCl [Sensipar]): Attach to the calcium receptor on the parathyroid gland and increase the sensitivity of receptors to serum calcium concentrations, thus reducing PTH values. Especially useful in patients with high calcium/phosphate concentrations and high PTH concentrations when vitamin D analogs cannot be used
- (a) The initial dose is 30 mg orally daily, irrespective of patient PTH concentration.
 - (b) Monitor serum calcium concentration every 1–2 weeks (risk of hypocalcemia is about 5%); do not initiate therapy if serum calcium concentration is less than 8.4 mg/dL.
 - (c) Can be used in patients irrespective of phosphate binder or vitamin D analog use
 - (d) Caution in patients with a seizure disorder (hypocalcemia may exacerbate)
 - (e) Adverse effects are nausea (30%) and diarrhea (20%).
 - (f) Cinacalcet inhibits cytochrome P450 (CYP) 2D6 metabolism, thereby inhibiting the metabolism of CYP2D6 substrates such that dose reductions in drugs with narrow therapeutic indexes may be required (e.g., flecainide, tricyclic antidepressants, thioridazine).
 - (g) Cinacalcet is primarily metabolized by CYP3A, so drugs that are potent inhibitors of CYP3A (ketoconazole) may increase cinacalcet concentrations by up to 2-fold.
 - (h) A recent study showed that cinacalcet did not lower the risk of death or major heart events in patients with CKD who were undergoing hemodialysis (N Engl J Med 2012;367:2482-94).

D. Other

1. Immunization: Vaccinations that may be needed include yearly influenza vaccine, pneumococcal vaccine, and hepatitis B vaccine.

VI. RENAL REPLACEMENT THERAPY

Patient Case

9. A 70-year-old man is being assessed for HD access. He has a history of DM and hypertension but is otherwise healthy. Which dialysis access has the lowest rate of complications and the longest life span and is thus the best access to use?

- A. Subclavian catheter.
- B. Tenckhoff catheter.
- C. Arteriovenous graft.
- D. Arteriovenous fistula.

A. Indications for Renal Replacement Therapy

- A – Acidosis (not responsive to bicarbonate)
- E – Electrolyte abnormality (hyperkalemia; hyperphosphatemia)
- I – Intoxication (boric acid; ethylene glycol; lithium; methanol; phenobarbital; salicylate; theophylline)
- O – Fluid overload (symptomatic [pulmonary edema])
- U – Uremia (pericarditis and weight loss)

B. Two Primary Modes of Dialysis

1. Hemodialysis—Most common modality
2. Peritoneal dialysis

C. Hemodialysis: Most Common Form of HD in the United States: Is in-center intermittent HD (usually three times weekly). Home-based HD (daily and nocturnal) is also used.

1. Access
 - a. Arteriovenous fistula—Preferred access!
 - i. Natural, formed by anastomosis of artery and vein
 - ii. Lowest incidence of infection and thrombosis, lowest cost, longest survival
 - iii. Takes weeks/months to “mature”
 - b. Arteriovenous graft
 - i. Synthetic (polytetrafluoroethylene)
 - ii. Often used for patients with vascular disease
 - c. Central venous catheters
 - i. Commonly used if permanent access unavailable or if dialysis is an emergency situation
 - ii. Problems include high infection and thrombosis rates. Low blood flow leads to inadequate dialysis.
2. Dialysis membranes
 - a. Conventional—Not used much anymore. Small pores. Made of cuprophane
 - b. High flux (large pores) and high efficiency (large surface area). Can remove drugs that were impermeable to standard membranes (vancomycin). A large amount of fluid removal (ultrafiltrate)

3. Adequacy
 - a. Kt/V —Unit-less variable. K = clearance, t = time on dialysis, and V = volume of distribution of urea. KDOQI set goal of 1.2 or more.
 - b. Urea reduction ratio (URR)
$$\text{URR} = \frac{[\text{PreBUN} - \text{PostBUN}]}{\text{PreBUN}} \cdot 100\%$$
4. Common complications of HD
 - a. Intradialytic
 - i. Hypotension—Primarily related to fluid removal. Common in elderly people and in people with DM. Treatment: Limit fluid gains between sessions; give normal or hypertonic saline. Less well-studied agents include fludrocortisone, selective serotonin reuptake inhibitors, levocarnitine, and midodrine. Of note, the FDA is currently evaluating whether midodrine will remain on the market (www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm225468.htm).
 - ii. Cramps—Vitamin E 400 international units daily (oral) has shown some benefit. Quinine was used widely in the past but is no longer recommended (controversial).
 - iii. Nausea/vomiting
 - iv. Headache/chest pain/back pain
 - v. Pruritus
 - vi. Restless legs syndrome. Treating iron deficiency and optimizing dialysis may help. Pharmacologic treatment is similar to that in the general population.
 - vii. Steal syndrome
 - b. Vascular access complications—Most common with catheters
 - i. Infection—Staphylococcus aureus. Need to treat aggressively. May need to remove catheter. Antimicrobial locks may be beneficial.
 - ii. Thrombosis—Suspected with low blood flow. Antiplatelet treatment may protect fistula from thrombosis or loss of patency, but has little or no effect on graft patency. Increased risk of bleeding. Can treat with alteplase in lumen
5. Factors that affect the efficiency of HD
 - a. Type of dialyzer used (changes in membrane surface area and pore size)
 - b. Length of therapy
 - c. Dialysis flow rate
 - d. Blood flow rate

D. Peritoneal Dialysis

1. The PD membrane is 1–2 m² (approximates the body surface area) and consists of the vascular wall, the interstitium, the mesothelium, and the adjacent fluid films. From 1.5 to 3 L of peritoneal dialysate fluid may be instilled in the peritoneum (fill), allowed to dwell for a specified time, and then drained.
2. Solutes and fluid diffuse across the peritoneal membrane. Glucose is the most commonly used osmotic agent in peritoneal dialysate. Glucose can be problematic in DM control, and it contributes to weight gain. Icodextrin (Extraneal) is a non-glucose, high-molecular-weight substance that can be used as an alternative for patients with diabetes. Of note, icodextrin can interfere with and cause falsely elevated glucose results, possibly leading to inappropriate therapy (specific glucometers are available).
3. PD is usually not used to treat AKI in adults.
4. Types of PD
 - a. Continuous ambulatory PD: Oldest form of PD; requires many manual changes throughout the day. Can be interruptive to daytime routine
 - b. Automated PD: Many variants exist, but continuous cycling PD is the most common. Patient undergoes many exchanges during sleep by a cycling machine. May have one or two dwells during day. Minimizes potential contamination. Lowest incidence of peritonitis

5. Peritonitis
 - a. Infection of the peritoneal cavity. Patient technique and population variables influence the infection rate. Elderly patients or those with diabetes have a higher infection rate. Peritonitis is a primary cause of the failure of PD.
 - b. Clinical presentation
 - i. Patients undergoing PD who present with cloudy effluent should be presumed to have peritonitis. Usually accompanied by abdominal pain.
 - ii. This is confirmed by obtaining effluent cell count, differential, and culture.
 - c. Treatment
 - i. The most common gram-positive organisms include *Staphylococcus epidermis*, *S. aureus*, and *Streptococcus*. The most common gram-negative organisms include *Escherichia coli* and *Pseudomonas aeruginosa*.
 - ii. The 2010 guidelines from the International Society of Peritoneal Dialysis state that empiric therapy must cover both gram-positive and gram-negative bacteria. Gram-positive organisms may be covered by vancomycin or a first-generation cephalosporin, and gram-negative organisms may be covered by a third-generation cephalosporin or aminoglycoside. Other combinations of medications have been studied and may be used according to local sensitivities. Intraperitoneal administration of antibiotics is preferred.
 - iii. Adjust antimicrobials according to culture and sensitivities.

VII. DOSAGE ADJUSTMENTS IN KIDNEY DISEASE

Patient Case

10. A 40-year-old patient receiving dialysis has a history of grand mal seizures. He takes phenytoin 300 mg daily. His albumin concentration is 3.0 g/dL. His total phenytoin concentration is 5.0 mg/dL. Which is the best interpretation of this patient's phenytoin concentrations?
 - A. The concentration is subtherapeutic, and a dose increase is warranted.
 - B. The concentration is therapeutic, and no dosage adjustment is needed.
 - C. The concentration is toxic, and a dose reduction is needed.
 - D. The concentration result is uninterpretable.

- A. Overview
 1. Dosing guidelines in package inserts are usually based on Cockcroft-Gault equation, and most studies were done before the creatinine assay was standardized. Thus, there is controversy regarding which method (Cockcroft-Gault, MDRD) should be used when adjusting doses.
 2. The National Kidney Disease Education Program of the National Institutes of Health/National Institute of Diabetes and Digestive and Kidney Diseases suggests that either GFR or CrCl be used for drug dosing. If using GFR in very large or small patients, the GFR should be multiplied by the actual body surface area to obtain GFR in milliliters per minute.
- B. Pharmacokinetic Principles Can Guide Therapy Adjustments
 1. Absorption—Oral absorption can be decreased.
 - a. Nausea and vomiting
 - b. Increased gastric pH (uremia)
 - c. Edema
 - d. Physical binding of drugs to phosphate binders

2. Distribution
 - a. Changes in concentrations in highly water-soluble drugs occur as extracellular fluid status changes (i.e., V_d is increased).
 - b. Acidic and neutral protein-bound drugs are displaced by toxin buildup. Other mechanisms include conformational changes of the plasma protein-binding site.
 - c. Phenytoin – Classical and clinically important example. The “normal” free fraction of phenytoin is 10%. Therapeutic range of phenytoin is 10–20 mg/L (1–2 mg/L free concentration). Free fraction can be as high as 25%–30% in patients with ESRD and hypoalbuminemia. So in a patient with ESRD with a free phenytoin concentration of 1.5 mg/L the laboratory may report a total phenytoin concentration of 6 mg/L. Incorrectly, some clinicians make dose adjustments to increase the total phenytoin concentration. Can assume a free fraction of 25% with these patients when evaluating total phenytoin concentrations. Alternatively, may check a measured free phenytoin concentration
 3. Metabolism—Variable changes can occur with uremia. Metabolites can accumulate.
 4. Excretion—Decreased
- C. General Recommendations
1. Patient history and clinical data
 2. Estimate CrCl (Jeliffe or Brater method in AKI; Cockcroft-Gault or MDRD study equations in stable kidney function).
 3. Identify medications that require modification (Table 3).

Table 3. Dose Adjustments in Decreased Kidney Function

Agent	Dose Adjustment
Antimicrobials	Almost all antibiotics will require dosage adjustment (some exceptions include cloxacillin, clindamycin, linezolid, metronidazole, erythromycin, azithromycin) Antiretrovirals: Individualize therapy: Monitor CD4 counts, viral load, and adverse effects (agents requiring dose adjustment: Lamivudine, adefovir, didanosine, stavudine, tenofovir, zalcitabine, emtricitabine, and zidovudine) Others: Acyclovir, valacyclovir, foscarnet, fluconazole, amantadine
Cardiac medications	Atenolol, ACEIs, digoxin, nadolol, sotalol; avoid potassium-sparing diuretics if CrCl < 30 mL/minute, higher-dose loop diuretics needed as CrCl declines; avoid thiazides at CrCl < 30 mL/minute (controversial); dabigatran, enoxaparin
Lipid-lowering therapy	Clofibrate, fenofibrate, most statins (monitor adverse events)
Pain medications	Caution with codeine, morphine, and tramadol because of accumulation; other agents may also accumulate; avoid meperidine because of seizure risk
Antipsychotic/antiepileptic agents	Chloral hydrate, gabapentin, pregabalin, lithium, paroxetine, primidone, topiramate, trazodone, vigabatrin
Hypoglycemic agents	Acarbose, chlorpropamide, glyburide, insulins, and metformin (risk of lactic acidosis); (insulin is commonly used in CKD; monitor blood glucose and adjust accordingly)
Miscellaneous	Allopurinol, colchicine, bisphosphonates, histamine-2 receptor antagonists, terbutaline; try to avoid all NSAIDs in CKD

ACEIs = angiotensin-converting enzyme inhibitors; CKD = chronic kidney disease; CrCl = creatinine clearance; NSAIDs = nonsteroidal anti-inflammatory drugs.

4. Identify or calculate drug doses individualized for the patient.
 - a. Tertiary sources (e.g., Micromedex) are a good first place to look. Sometimes different sources have different recommendations so in critical medication issues, may need to be diligent.
 - b. Published data. Would be unusual to have to go to primary literature. More likely might need to call company for dosing information
 5. Monitor patient (e.g., kidney function, clinical values) and drug concentration (if applicable).
 6. Revise regimen as appropriate.
- D. Drug Dosing in HD
1. Dosing changes for patients receiving HD may be necessary because of accumulation caused by kidney failure AND/OR because the procedure may remove the drug from the circulation.
 2. The following drug-related factors affect drug removal during dialysis:
 - a. Molecular weight (MW)—With conventional dialysis membranes, larger-molecule drugs (greater than 500 Da MW) do not pass through the membranes; thus, they are not removed. With high-flux membranes, molecules of up to 20,000 Da MW are removed. So with high-flux HD, vancomycin (1480 Da MW) is removed. Because albumin has an MW of 50,000, it would not be removed by any type of hemodialysis membrane.
 - b. Water soluble—Non-water-soluble drugs not likely removed
 - c. Protein binding—Because albumin cannot pass through membranes, protein-bound drugs cannot pass either.
 - d. Volume of distribution—Drugs with a small V (less than 1 L/kg) are present in the central circulation/compartments for removal. Drugs with large V s (e.g., digoxin and tricyclic antidepressants) are not effectively removed by dialysis.
 3. Procedure-related factors affecting drug removal
 - a. Type of dialyzer—High flux widely used now
 - b. Blood flow rate: Increased rates will increase delivery and maintain the gradient across membranes.
 - c. Duration of dialysis session
 - d. Dialysate flow rate: High flow rates will increase removal by maintaining the gradient across membranes.

VIII. KIDNEY STONES (NEPHROLITHIASIS)

- A. Reported Annual Incidence: 100 per 100,000 men and 36 per 100,000 women; 12% of men and 5% of women will develop a symptomatic stone by age 70 years
- B. Rates of Nephrolithiasis
 1. Prevalence is higher in men than in women and in white than in African American people.
 2. Recurrence rate is high after lithotripsy.
- C. Eighty Percent of Stones Contain Calcium (oxalate most common, phosphate less common). Other stones are often caused by metabolic disorders; they contain uric acid, struvite (magnesium ammonium phosphate), cystine.

- D. Prevention of Idiopathic Calcium Kidney Stones
1. Low-calcium and low-oxalate diet—Reduces substrate to form the stone
 2. Hydration—Dilutes calcium so that stones are less likely to precipitate
 3. Potassium citrate—Citrate moiety combines with calcium in the urine, preventing the formation of crystals. Citrate also raises urinary pH, preventing uric acid or cystine kidney stones from forming.
 4. Thiazide diuretics—Reduce urinary calcium excretion
 5. Allopurinol—Reduces uric acid production but may also be useful in preventing the formation of some calcium-containing stones
- E. Treatment of Existing Kidney Stones
1. Guidelines published by the American Urological Association (www.auanet.org)
 2. Stones less than 5 mm likely to pass within 1 month; lithotripsy commonly used otherwise
 3. Pain can be severe. Treat with NSAIDs as medications of choice. Opioids for severe pain. Thiazides may be used to reduce stone formation in patients with hypercalciuria.

REFERENCES

Acute Kidney Injury

1. Dager W, Halilovic J. Acute renal failure. In: DiPiro JT, Talbert RL, Yee GC, et al., eds. *Pharmacotherapy: A Pathophysiologic Approach*, 8th ed. New York: McGraw-Hill, 2011:741-66.
2. Stamatakis MK. Acute kidney injury. In: Chisholm-Burns MA, Wells BG, Schwinghammer TL, et al., eds. *Pharmacotherapy: Principles and Practice*. New York: McGraw-Hill, 2013:chap 25.
3. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO clinical practice guideline for acute kidney injury. *Kidney Int Suppl* 2012;2:1-138.

Drug-Induced Kidney Damage

1. Nolin TD, Himmelfarb J. Drug-induced kidney disease. In: DiPiro JT, Talbert RL, Yee GC, et al., eds. *Pharmacotherapy: A Pathophysiologic Approach*, 8th ed. New York: McGraw-Hill, 2011:819-36.

Chronic Kidney Disease: Complications and Management*General*

1. Derebail VK, Kshirsagar AV, Joy MS. Chronic kidney disease: progression-modifying therapies. In: DiPiro JT, Talbert RL, Yee GC, et al., eds. *Pharmacotherapy: A Pathophysiologic Approach*, 8th ed. New York: McGraw-Hill, 2011:767-86.
2. Hudson JQ. Chronic kidney disease: management of complications. In: DiPiro JT, Talbert RL, Yee GC, et al., eds. *Pharmacotherapy: A Pathophysiologic Approach*, 8th ed. New York: McGraw-Hill, 2011:787-816.
3. Schonder KS. Chronic and end-stage renal disease. In: Chisholm-Burns MA, Wells BG, Schwinghammer TL, et al., eds. *Pharmacotherapy: Principles and Practice*. New York: McGraw-Hill, 2013:chap 26.
4. Levey AS, Coresh J. Chronic kidney disease. *Lancet* 2012;379:165-80.
5. Levey AS, de Jong PE, Coresh J, et al. The definition, classification, and prognosis of chronic kidney disease: a KDIGO controversies report. *Kidney Int* 2011;80:17-28.

Blood Pressure

1. National Kidney Foundation. KDOQI clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease. *Am J Kidney Dis* 2004;43(5 suppl 1):S1-290.
2. Kidney Disease: Improving Global Outcomes (KDIGO) Blood Pressure Work Group. KDIGO clinical practice guideline for the management of blood pressure in chronic kidney disease. *Kidney Int Suppl* 2012;2:337-414.

Diabetes

1. National Kidney Foundation. KDOQI clinical practice guidelines for diabetes and CKD: 2012 update. *Am J Kidney Dis* 2012;60:850-886.
2. Bakris GL. Treatment of diabetic nephropathy. In: UpToDate. Glassock RJ, Nathan DM, eds. UpToDate. Waltham, MA. (Accessed on November 1, 2014.)

Complications (Anemia/Bone Disease)

1. National Kidney Foundation. KDOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. *Am J Kidney Dis* 2003;42(4 suppl 3):S1-201.
2. KDOQI; National Kidney Foundation. KDOQI clinical practice guidelines and clinical practice recommendations for anemia in chronic kidney disease. *Am J Kidney Dis* 2006;47(5 suppl 3):S11-145.
3. KDIGO CKD-MBD Work Group. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD). *Kidney Int* 2009;76 (suppl 113):S1-130.
4. Quarles LD, Cronin RE. Management of secondary hyperparathyroidism and mineral metabolism abnormalities in dialysis patients. In: UpToDate. Goldfarb S, ed. UpToDate, Waltham, MA. (Accessed November 1, 2014).
5. Quarles LD, Cronin RE. Management of secondary hyperparathyroidism and mineral metabolism abnormalities in adult predialysis patients with chronic kidney disease. In: UpToDate. Goldfarb S, ed. UpToDate, Waltham, MA. (Accessed November 1, 2014).

6. Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group. KDIGO clinical practice guideline for anemia in chronic kidney disease. *Kidney Int Suppl* 2012;2:279-335.

Renal Replacement Therapy

1. Sowinski KM, Churchwell MD. Hemodialysis and peritoneal dialysis. In: DiPiro JT, Talbert RL, Yee GC, et al., eds. *Pharmacotherapy: A Pathophysiologic Approach*, 8th ed. New York: McGraw-Hill, 2011:817.
2. Li PK, Szeto CC, Piraino B, et al. Peritoneal dialysis-related infections recommendations: 2010 update. *Perit Dial Int* 2010;30:393-423.

Drug Therapy Adjustment in CKD

1. Matzke GR. Drug therapy individualization for patients with chronic kidney disease. In: DiPiro JT, Talbert RL, Yee GC, et al., eds. *Pharmacotherapy: A Pathophysiologic Approach*, 8th ed. New York: McGraw-Hill, 2011:861-72.
2. Chronic Kidney Disease and Drug Dosing. Information for Providers (Revised January 2010). Available at www.nkdep.nih.gov/professionals/drug-dosing-information.htm. Accessed September 28, 2012.
3. Matzke GR, Arnoff GR, Atkinson AJ, et al. Drug dosing consideration in patients with acute and chronic kidney disease—a clinical update from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int* 2011;80:1122-37.

Nephrolithiasis

1. Worcester EM, Coe FL. Calcium kidney stones. *N Engl J Med* 2010;363:954-63.
2. Brener ZZ, Winchester JF, Salman H, et al. Nephrolithiasis: evaluation and management. *South Med J* 2011;104:133-9.

ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. Answer: B

The patient has stage 3 CKD (GFR 30–59 mL/minute/1.73 m²), which can be calculated by the MDRD, CKD-EPI, or Cockcroft-Gault equation. The five stages range from mild kidney damage (stage 1) to kidney failure (stage 5). A modified classification scheme has been released by KDIGO, though it is not yet widely used in the United States. This patient would have CKD stage G3a according to KDIGO.

2. Answer: D

Clinicians should be aware that all creatinine-based equations to estimate kidney function will provide overestimations if the SCr is low because the patient has low muscle mass. Some clinicians “round up” the SCr in these patients to 0.8 or 1.0 mg/dL, but there are no data to support this arbitrary approach; thus, it should be avoided. If an accurate measure of kidney function is needed, a 24-hour collection for CrCl should be ordered.

3. Answer: B

The patient’s BP is not at goal (should be less than 130/80 mm Hg). To improve BP control and enhance the effect of the ACEI, chlorthalidone should be added to the regimen (Answer B). Adding chlorthalidone will also counter the tendency for hyperkalemia. Monitoring of SCr and serum potassium concentration is appropriate for this patient. There is less than a 30% increase in SCr, so enalapril should be continued, making Answer A and Answer C inappropriate. Increasing atenolol (Answer D) would probably lower BP but is not the preferred route because renal protection would likely not be enhanced.

4. Answer: C

This patient has stage 5 CKD, so anemia caused by EPO deficiency should be high on the differential diagnosis (Answer C). Although iron deficiency (Answer A) can be quite common in patients with CKD, this patient’s iron study results are in the normal range. A dietary deficiency causing anemia (Answer B) is usually iron deficiency. Angiotensin-converting enzyme inhibitors (Answer D) have been linked to epoetin resistance, but the effect is unlikely to be this dramatic.

5. Answer: B

From the laboratory values, this patient has an iron deficiency, making Answer D incorrect. Oral iron (Answer A) is not recommended for patients undergoing dialysis because it is generally ineffective and has significant GI adverse effects and drug interactions. Increasing the epoetin dose (Answer C) might increase the hemoglobin concentration, but excessive doses of epoetin would be needed, which would not be cost-effective. Intravenous iron (Answer B) should be administered.

6. Answer: B

Hyperparathyroidism is associated with epoetin resistance in patients receiving HD (Answer B). Although iron deficiency is the most common cause of epoetin deficiency, the laboratory results for this patient do not indicate iron deficiency (Answer A). Phenytoin therapy (Answer C) has been associated with folate deficiency in other patient populations but not in patients receiving HD. Infection (Answer D) and inflammation are very common causes of epoetin deficiency in patients undergoing HD, but there is nothing in this patient’s presentation to suggest an infectious or inflammatory process.

7. Answer: B

This patient requires treatment for elevated iPTH concentration, which puts him at high risk of renal osteodystrophy. He has high serum phosphorus and calcium values. The corrected calcium concentration is 10.2 mg/dL. Current binder therapy is contributing to excessive calcium exposure; therefore, calcium acetate should be discontinued and sevelamer, initiated. Moreover, cinacalcet will lower iPTH and potentially serum calcium values, making Answer B correct. Answer A is incorrect because increasing the intake of calcium acetate may worsen the patient’s hypercalcemia. Answer C is incorrect for two reasons. First, the patient requires some type of phosphate binder; second, intravenous vitamin D analogs can worsen hypercalcemia and are not very effective at reducing elevated iPTH values in the presence of hyperphosphatemia. Answer D is incorrect because intravenous vitamin D analogs can worsen hypercalcemia and are not very effective at reducing elevated iPTH values in the presence of hyperphosphatemia.

8. Answer: A

This patient has hyperphosphatemia. Other than serum phosphorus, his laboratory values are normal. Because dietary restrictions of phosphorus have been insufficient, a phosphate binder is required. The medications in Answer A, Answer B, and Answer C are all phosphate binders and would work. However, calcium acetate and sevelamer are very expensive (Answer B and Answer C), and this patient is without health insurance. Even with health insurance, sevelamer would probably be considered inappropriate because the patient could benefit from calcium. Therefore, Answer A, calcium carbonate, is correct. Calcitriol (Answer D) is sometimes used for patients with CKD to raise serum calcium concentration; however, this patient's calcium concentration is not low.

9. Answer: D

A native arteriovenous fistula is the preferred access for chronic HD (Answer D). If an arteriovenous fistula cannot be constructed, a synthetic arteriovenous graft (Answer C) is considered second line. A subclavian catheter (Answer A) is a poor choice because of the increased risk of infection and thrombosis and because of the poor blood flow obtained through a catheter. Catheter use should be limited to emergency and short-term situations as well as when all other access options have been exhausted. A Tenckhoff catheter (Answer B) is incorrect because it is used for PD.

10. Answer: B

The presence of kidney failure and low albumin concentration results in an increased free fraction of phenytoin. Using the correction equation gives a corrected concentration of 12.5 mg/L, which is therapeutic. A free phenytoin concentration can also be obtained.

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. Answer: D

This patient's PTH, calcium, and phosphorus values are not at goal. Answer A is not the best choice because it would add more calcium load and is above the recommended daily calcium dose. Answer B similarly gives a calcium product to someone whose calcium concentration is too high already. Aluminum (Answer C) should be avoided in patients with CKD because of the risk of aluminum intoxication. Answer D, sevelamer, is the best choice because it lowers phosphorus while avoiding additional calcium administration. Sevelamer dosage may need to be adjusted to reduce phosphate concentrations to goal.

2. Answer: B

Cinacalcet is a good choice for this patient because both the high calcium and phosphorus values limit the use of any vitamin D analog. However, serum calcium values (Answer B) should be monitored closely because hypocalcemia can occur. Hypocalcemia can lead to seizures (most likely in patients with a history of them), and QT prolongation. Parathyroid hormone (Answer C) should also be monitored because its concentration should decrease, but this is a sign of efficacy. Liver function tests may be performed, but serious liver problems are rare. Creatinine need not be monitored in a patient already receiving dialysis.

3. Answer: A

This patient's anemia has worsened while receiving epoetin therapy, most likely because of iron deficiency. Answer A is a recommended iron-loading regimen. Patients undergoing dialysis universally require parenteral iron to maintain iron stores. Oral iron (Answer B) is not recommended in patients receiving HD. It is unlikely to provide sufficient iron to overcome the anemia and replenish body stores. Folic acid (Answer C) is already being administered to this patient with her renal multivitamin, and it does not address the primary problem of iron deficiency. Although increasing the epoetin dose (Answer D) might increase the patient's hemoglobin concentration, it is not appropriate without first addressing the patient's iron deficiency. In addition, it will increase dialysis-related costs with very little benefit to the patient.

4. Answer: C

For a drug to be dialyzed, it should be water soluble, ruling out Answer A and Answer D. In addition, drugs with relatively large volumes of distribution (Answer B) are not effectively removed by dialysis because the drug is in the tissues. With high-flux membranes, molecules of up to 20,000 Da MW are removed, so MW is not an issue with any of these drugs. Consequently, drug C is most likely to be removed by dialysis.

5. Answer: D

This patient shows the classic signs and symptoms of PD-associated peritonitis. Immediate treatment is indicated. Empiric therapy must cover both gram-positive species (*Staphylococcus* spp. and *Streptococcus* spp.) and gram-negative species (including *Pseudomonas* spp.). Answer D is best at covering both, and the drugs are administered by the preferred, intraperitoneal route. Answer A uses oral medications and provides insufficient gram-positive coverage. In addition, the anaerobic coverage provided by metronidazole is not recommended for empiric treatment of PD-related peritonitis. Answer B provides only gram-positive coverage. Answer C is incorrect because it has inadequate gram-positive coverage and uses the intravenous route. Intraperitoneal aminoglycosides may be used in peritonitis, but for no longer than 2 weeks because of the risk of ototoxicity and nephrotoxicity (in patients with residual kidney function).

6. Answer: B

Although this patient might require treatment for hyperglycemia (Answer A), metformin is contraindicated in a man with an SCr greater than 1.5 mg/dL. The presence of macroalbuminuria in type 2 DM indicates that an ACEI or ARB (Answer B) is needed to reduce intraglomerular pressure and slow kidney disease progression. Because this patient's BP is above goal, lowering it would be beneficial. However, neither metoprolol nor amlodipine (Answer C and Answer D) decreases proteinuria significantly.

7. Answer: A

Protein restriction (Answer A) to 0.8 g/kg/day or less will likely reduce albuminuria and is the best choice. Omega-3 fatty acids (Answer B) have not been studied in diabetic kidney disease. Atkins diet (Answer C) is not recommended because it tends to be a high-protein diet. Low-potassium diets (Answer D) would be appropriate for a patient with advanced kidney disease (not this patient) to prevent hyperkalemia but would not affect disease progression.

8. Answer: B

This is a fairly classic presentation of hemodynamically mediated AKI (Answer B). In this case, the NSAID is inhibiting vasodilating prostaglandins in the afferent arteriole. Prerenal kidney injury (Answer A) refers to abrupt changes in kidney function caused by low-flow states to the kidney (e.g., hypotension). Intrinsic AKI (Answer C) includes ATN and AIN. The presentation and a urinalysis confirming absence of cellular casts rule out this option. Postrenal failure (Answer D) is usually caused by obstruction, and there is no reason to suspect obstruction in this patient.