Chapter 75: Chronic Kidney Disease

INTRODUCTION

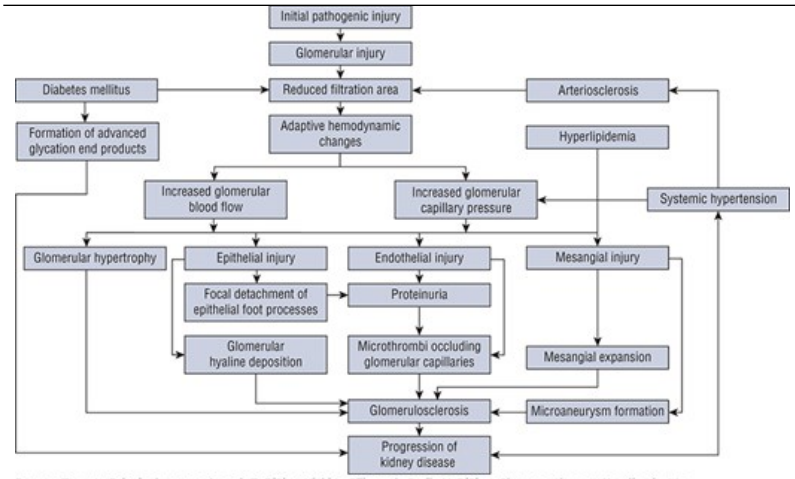
- *Chronic kidney disease* (CKD) is defined as abnormalities in kidney structure or function, present for 3 months or longer.
- CKD is classified by glomerular filtration rate (GFR) and urinary albumin-to-creatinine ratio (uACR) based on the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines for evaluation and management of CKD. The KDIGO classification system is referred to as CGA staging (*c*ause, *G*FR, *a*lbuminuria).
- A patient is classified with end-stage renal disease (ESRD) when their GFR is below 15 mL/min/1.73 m^2 (0.14 mL/sec/m^2) and either chronic dialysis or kidney transplantation is needed to sustain life. KDIGO classification will be used in this chapter; the term CKD 5D indicates a patient with ESRD requiring dialysis as either hemodialysis (CKD 5HD) or peritoneal dialysis (CKD 5PD).
- Prognosis of CKD depends on cause of kidney disease, GFR at time of diagnosis, degree of albuminuria measured by uACR, and presence of other comorbid conditions. Please refer to *Pharmacotherapy: A Pathophysiologic Approach*, 11th ed., Chapter 61, Figure 61-1: KDIGO GFR and albuminuria categories and prognosis of CKD by category.

PATHOPHYSIOLOGY

- Clinical and sociodemographic risk factors for susceptibility to and initiation of CKD are useful for identifying individuals at risk of developing CKD. Clinical factors include, but aren't limited to, diabetes, hypertension, obesity, autoimmune diseases, systemic infections, family history of CKD, reduction in kidney mass, and low birth weight. Sociodemographic factors include older age, US ethnic minority status, low income or education, and exposure to certain chemical and environmental conditions.
- KDIGO recommends that prognosis be considered to help guide testing and treatment decisions. Validated estimating equations such as the kidney failure risk equation (KFRE) provide an accurate 2- and 5-year risk of progression to kidney failure for individuals with stage 3–5 CKD.
- Progression risk factors are associated with further decline in kidney function. Persistence of the underlying initiation factors (eg, diabetes mellitus, hypertension, glomerulonephritis) appears to be the most important predictor of progressive CKD.
- Most progressive nephropathies share a final common pathway to irreversible renal parenchymal damage and ESRD (**Figure 75-1**). Key elements of the pathway to ESRD include loss of nephron mass, glomerular capillary hypertension, and proteinuria.

FIGURE 75-1

Proposed mechanisms for progression of kidney disease.



CLINICAL PRESENTATION

- Progression of CKD from category 1 to 5 occurs over decades in the majority of people who are asymptomatic until they reach CKD 4 or 5. Signs and symptoms seen with stages 4–5 include fatigue, weakness, shortness of breath, mental confusion, nausea, vomiting, bleeding, anorexia, itching, cold intolerance, peripheral neuropathies, edema, weight gain, changes in urine output, and “foaming” of urine.

TREATMENT OF CKD

General Approach

- Goals of Treatment: The goal is to delay or prevent the progression of CKD while minimizing the development or severity of complications.
- Management should be based on KDIGO consensus guidelines to provide both evidence and opinion to optimize management of CKD.
- General nonpharmacologic recommendations for all CKD patients include exercise 30 minutes five times/week, weight loss if BMI >25 kg/m^2, smoking cessation, limit alcohol intake, and follow a low-sodium diet if hypertensive.
- General pharmacologic recommendations for all CKD patients include to adjust medication doses for kidney function, avoid herbal medicines, discuss over-the-counter medicines with pharmacist or other provider before self-medicating, discontinue potentially nephrotoxic/renally excreted drugs if estimated GFR (eGFR) <60 mL/min/1.73 m^2, adhere to vaccine recommendations, take aspirin as secondary prevention if indicated, and avoid oral phosphate-containing bowel preparations if GFR <60 mL/min/1.73 m^2.

Pharmacologic Therapy

- Pharmacologic therapies to slow CKD progression include drugs with demonstrated benefits to reduce proteinuria and to manage the causal factors for CKD, primarily hypertension and diabetes.

Proteinuria

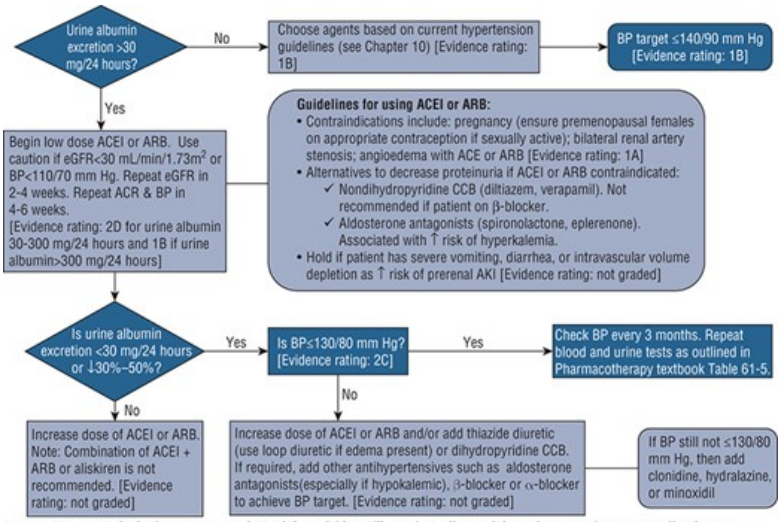
- First-line therapy for patients with diabetic CKD (DCKD) should include an **angiotensin-converting enzyme inhibitor (ACEI)** or an **angiotensin II receptor blocker (ARB)** if the patient’s urine albumin excretion is in category A2 or greater (uACR between 30 and 300 mg/g [3–34 mg/mmol]). The antiproteinuric effect of ACEIs and ARBs is a class effect. Initiate therapy with the lowest recommended dose and increase dose until albuminuria is reduced by 30%–50% or side effects such as a greater than 30% decrease in eGFR or elevation in serum potassium occur (**Figure 75-2**).
- Achieving the target blood pressure is the primary goal for CKD patients with hypertension and a secondary goal is to control proteinuria.

- **Nondihydropyridine calcium channel blockers** are second- or third-line antiproteinuric drugs when an ACEI or ARB is contraindicated or not tolerated.
- Sodium glucose transport-2 inhibitors (SGLT-2) slow progression of DCKD by reducing glucose and sodium reabsorption in the proximal tubule of the kidney, resulting in a decrease in glomerular hyperfiltration and glomerular hypertension. In one trial **empagliflozin** reduced albuminuria, slowed eGFR decline, and reduced risk for progression to ESRD by 50% in patient with eGFR ≥30 mL/min/1.73 m^2.

FIGURE 75-2

Treatment of hypertension in chronic kidney disease. (*Data from 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.*)

(ACEI, angiotensin-converting enzyme inhibitor; ACR, albumin-to-creatinine ratio; AKI, acute kidney injury; ARB, angiotensin receptor blocker; BP, blood pressure; CCB, calcium channel blocker; eGFR, estimated glomerular filtration rate.)



Hypertension

- **Figure 75-2** provides an algorithm for recommended blood pressure goals based on the degree of albuminuria present and the choice of antihypertensive agent.
- For more information on hypertension, see Chapter 10.

Diabetes

- Screen patients with diabetes annually for CKD starting at the time of diagnosis of type 2 diabetes and 5 years after diagnosis of type 1 diabetes by ordering serum creatinine, eGFR, and uACR.
- Management of diabetes in patients with CKD includes reduction of proteinuria and achievement of target blood pressure and A1C.
- For more information on diabetes, see Chapter 19.

Treatment of Secondary Complications

Anemia of CKD

- Desired outcomes of anemia management are to increase oxygen-carrying capacity, decrease signs and symptoms of anemia, and decrease the

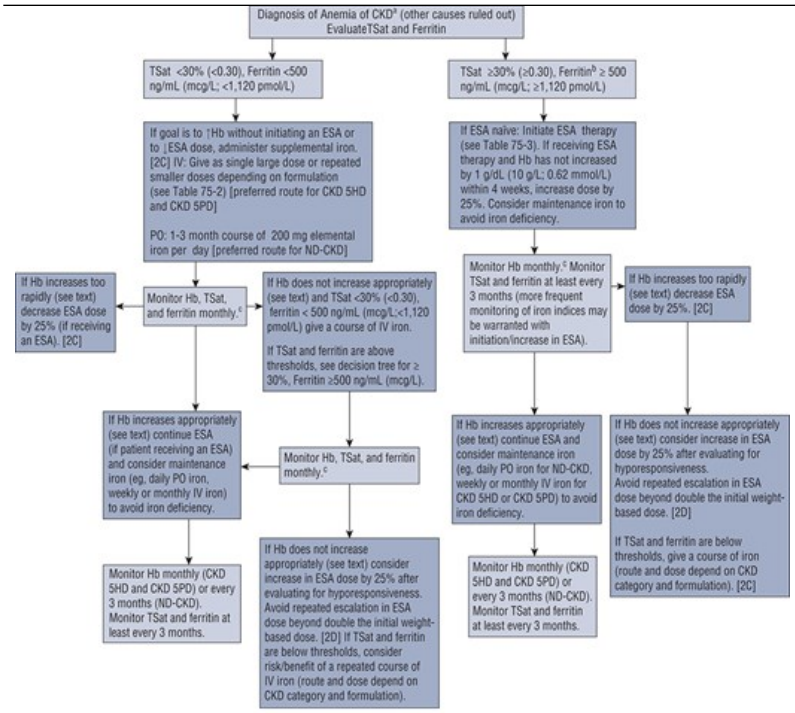
need for blood transfusions.

- Guide initiation of iron or erythropoiesis-stimulating agent (ESA) therapy by the patient's hemoglobin (Hb), transferrin saturation (TSat), and ferritin (**Table 75-1**). The risk of mortality and cardiovascular events is higher in CKD patients treated to higher Hb target values with an ESA. The target range for Hb in the CKD population is a topic of much debate.
- Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines suggest a Hb range of 11–12 g/dL (110–120 g/L; 6.83–7.45 mmol/L) for all CKD patients, a target TSat of greater than 20% (>0.20), and a serum ferritin of greater than 100 ng/mL (mcg/L; >225 pmol/L) for CKD patients not requiring HD and greater than 200 ng/mL (mcg/L; >450 pmol/L) for CKD 5HD patients.
- Oral or IV **iron** supplementation is recommended in non-HD patients (eg, CKD category 3 or higher and PD patients). Supplementation with oral products (see Table 33-2) is more convenient but patients are likely to require IV iron supplementation to correct absolute iron deficiency, especially if they are receiving an ESA. Adverse effects of oral iron are primarily GI in nature and include constipation, nausea, and abdominal cramping which may negatively influence adherence.
- Soluble **ferric pyrophosphate citrate** is an iron compound added to the dialysate used for HD allowing for continuous iron administration during the procedure. Ferric pyrophosphate binds directly to transferrin, bypassing the reticuloendothelial system. The role of this agent in treating anemia of CKD is evolving.
- IV iron preparations have different pharmacokinetic profiles determined by the size of the iron-containing core and the composition of the surrounding carbohydrate shell (**Table 75-2**).
- Adverse effects of IV iron include allergic reactions, hypotension, dizziness, dyspnea, headaches, lower back pain, arthralgia, syncope, and arthritis. Some of these reactions can be minimized by decreasing the dose or rate of infusion. Non-dextran IV iron formulations have a better safety record than iron dextran. An analysis of anaphylaxis risk in patients newly exposed to IV iron products (including **dextran**, **gluconate**, **sucrose**, or **ferumoxytol**) reported the highest risk with iron dextran and the lowest risk with iron sucrose.
- Long-term IV iron administration introduces a risk of iron overload leading to hepatic, pancreatic, and cardiac dysfunction. Maintain target serum ferritin and TSat values to minimize risk.
- All available ESAs may be administered either IV or subcutaneously (SC) (**Table 75-3**). The biosimilar **epoetin-alfa epbx** is available in the United States with the same indications as the biological drug, **epoetin alfa**. SQ administration of epoetin results in a prolonged absorption phase leading to an extended half-life allowing target Hb to be maintained at doses 15%–30% lower than IV doses.
- The prolonged half-lives of **darbepoetin alfa** and **methoxy PEG-epoetin beta** allow for less frequent dosing.
- Causes of ESA resistance include iron deficiency, acute illness, inflammation, infection, chronic bleeding, aluminum toxicity, malnutrition, hyperparathyroidism, cancer, and chemotherapy.
- ESAs are well tolerated. Hypertension is the most common adverse event.
- **Figure 75-3** provides an approach to management of anemia in patients with CKD. For more information on anemia, see Chapter 33.

FIGURE 75-3

Algorithm for management of anemia of CKD in adults.

(CKD, chronic kidney disease; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; ND-CKD, nondialysis CKD patients; TSat, transferrin saturation.)



[a]See Table 75-1 and text for discussion of Hb levels.
[b]Clinical judgment should be used to determine if iron supplementation should be continued when ferritin >500 ng/mL (mcg/L; 1120 pmol/L).
[c]Weekly monitoring of Hb may be warranted. Wait at least 1 week after an IV dose of iron to measure TSat and ferritin.

Source: Terry L. Schwinghammer, Joseph T. DiPiro, Vicki L. Ellingrod, Cecily V. DiPiro: *Pharmacotherapy Handbook, 11e*

TABLE 75-1

KDIGO Recommendations for Initiation of Erythropoiesis-Stimulating Agents and Iron in Anemia of Chronic Kidney Disease

	ND-CKD	CKD 5HD and CKD 5PD	Pediatric CKD
ESA initiation	If Hb <10 g/dL (100 g/L; 6.21 mmol/L). Consider rate of fall of Hb, prior response to iron, risk of needing a transfusion, risk of ESA therapy, and presence of anemia symptoms before initiating an ESA. [2C] Do not initiate if Hb ≥10 g/dL (100 g/L; 6.21 mmol/L). [2D]	Use ESAs to avoid drop in Hb to <9 g/dL (90 g/L; 5.59 mmol/L) by starting an ESA when Hb is between 9 and 10 g/dL (90 and 100 g/L; 5.59 and 6.21 mmol/L). [2B]	Selection of Hb concentration at which to initiate ESA therapy should include consideration of potential benefits (eg, improvement in QOL, school attendance, avoidance of blood transfusions) and potential harms. [2D]
Hb level	Do not use ESAs to *intentionally* increase Hb above 13 g/dL (130 g/L, 8.07 mmol/L). [1A] Do not use ESAs to maintain Hb above 11.5 g/dL (115 g/L; 7.14 mmol/L). [2C]	Do not use ESAs to *intentionally* increase Hb above 13 g/dL (130 g/L, 8.07 mmol/L). [1A] Do not use ESAs to maintain Hb above 11.5 g/dL (115 g/L; 7.14 mmol/L). [2C]	Suggest Hb range of 11–12 g/dL (110–120 g/L, 6.83–7.45 mmol/L). [2D]
Iron initiation[a]	If TSat is ≤30% (0.30) and ferritin is ≤500 ng/mL (mcg/L; 1120 pmol/L). [2C]	If TSat is ≤30% (0.30) and ferritin is ≤500 ng/mL (mcg/L; 1120 pmol/L). [2C]	If TSat is ≤20% (0.20) and ferritin is ≤100 ng/mL (mcg/L; 225 pmol/L). [1D]

[a]If TSat and serum ferritin are below suggested levels, consider iron supplementation if goal is to increase Hb and/or decrease ESA dose. *Note*: Serum ferritin is an acute-phase reactant—use clinical judgment when above 500 ng/mL (mcg/L; 1120 pmol/L).

CKD, chronic kidney disease; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; ND-CKD, nondialysis CKD patients; QOL, quality of life; TSat, transferrin saturation.

The strength of recommendation is indicated as Level 1, Level 2, or Not Graded. The quality of the supporting evidence is shown as A, B, C, or D.

TABLE 75-2

IV Iron Preparations

Iron Compounds	Brand Names	Half-Life (Hours)	Molecular Weight (Daltons)	FDA-Approved Indications	FDA-Approved Dosing[a]	Dose Ranges (mg)[b,c]
Ferric carboxymaltose	Injectafer	7–12	150,000	Adult patients with intolerance to oral iron or who have had an unsatisfactory response to oral iron and in adult patients with CKD not on dialysis	Give 2 doses separated by at least 7 days of 750 mg per dose (if body weight is ≥50 kg) or 15 mg/kg per dose (if body weight is <50 kg) not to exceed 1500 mg per course. Give either IV push (100 mg/min) or diluted in not more than 250 mL of 0.9 NaCl as an infusion over at least 15 minutes	750
Ferumoxytol	Feraheme	15	750,000	Adult patients with intolerance to oral iron or	510 mg (17 mL) as a single dose, followed by a second 510 mg dose 3–8 days after the initial dose.	510

				who have had an unsatisfactory response to oral iron and in adult patients with CKD	Dilute in 50–200 mL of 0.9% NaCl or 5% dextrose and administer as an IV infusion over 15 minutes	
Iron dextran	INFeD	40–60	96,000	Patients with iron deficiency in whom oral iron is unsatisfactory or impossible	100 mg over 2 minutes (25 mg test dose required) Note: equation provided by manufacturer to calculate dose based on desired Hb	25–1000
Iron sucrose	Venofer	6	43,000	Adult and pediatric CKD 5HD patients aged 2 years and older	Adult: 100 mg over 2–5 minutes or 100 mg in maximum of 100 mL of 0.9% NaCl over 15 minutes per consecutive HD session Pediatric: 0.5 mg/kg not to exceed 100 mg per dose over 5 minutes or diluted in 25 mL of 0.9% NaCl administered over 5–60 minutes (give dose every 2 weeks for 12 weeks)	25–1000
				Adult and pediatric ND-CKD patients aged 2 years and older	Adult: 200 mg over 2–5 minutes on five different occasions within 14-day period. There is limited experience with administration of 500 mg diluted in a maximum of 250 mL of 0.9% NaCl over 3.5–4 hours on day 1 and day 14 Pediatric: see pediatric dosing for CKD 5HD (give dose every 4 weeks for 12 weeks)	
				Adult and pediatric CKD 5PD patients aged 2 years and older	Adult: give 3 divided doses within 28 days as 2 infusions of 300 mg over 1.5 hours 14 days apart followed by one 400 mg infusion over 2.5 hours 14 days later. Dilute in a maximum of 250 mL of 0.9% NaCl Pediatric: see pediatric dosing for CKD 5HD (give dose every 4 weeks for 12 weeks)	
Sodium ferric gluconate	Ferrlecit	1	350,000	Adult and pediatric CKD 5HD patients aged 6 years and older receiving ESA therapy	Adult: 125 mg over 10 minutes or 125 mg in 100 mL of 0.9% NaCl over 60 minutes per HD session Pediatric: 1.5 mg/kg in 25 mL of 0.9% NaCl over 60 minutes per dialysis session; maximum dose 125 mg per dose	62.5–1000

[a]Monitor for 30 minutes following an infusion; KDIGO guidelines recommend monitoring for 60 minutes (1B recommendation for iron dextran, 2C recommendation for non-dextran products).

[b]Dose ranges for iron deficiency in CKD. With the exception of ferric carboxymaltose and ferumoxytol, small doses (eg, 25–150 mg/week) are generally used for maintenance regimens. Larger doses (eg, 1 g) should be administered in divided doses.

[c]Total dose for absolute iron deficiency is approximately 1 g in divided doses (1.5 g for ferric carboxymaltose).

CKD, chronic kidney disease; ESA, erythropoiesis-stimulating agent; ND-CKD, nondialysis CKD patients.

TABLE 75-3

Erythropoiesis-Stimulating Agents in Chronic Kidney Disease

Drug Name	Brand Name(s)	Starting Dose	Route of Administration	Half-Life (Hours)
Epoetin alfa	Epogen, Procrit	Adults: 50–100 units/kg three times per week Pediatrics: 50 units/kg three times per week	IV or SC	8.5 (IV) 24 (SC)
Epoetin alfa-epbx	Retacrit	See epoetin alfa information		
Darbepoetin alfa	Aranesp	Adults: ND-CKD: 0.45 mcg/kg once every 4 weeks CKD 5HD or CKD 5PD: 0.45 mcg/kg once per week or 0.75 mcg/kg every 2 weeks Pediatrics: 0.45 mcg/kg once weekly; may give 0.75 mcg/kg once every 2 weeks in ND-CKD patients	IV or SC	25 (IV) 48 (SC)
Methoxy PEG-epoetin beta	Mircera	All adult CKD patients: 0.6 mcg/kg every 2 weeks; once Hb stabilizes, double the dose and administer monthly (eg, if administering 0.6 mcg/kg every 2 weeks, give 1.2 mcg/kg every month)	IV or SC	134 (IV) 139 (SC)

CKD, chronic kidney disease; ND-CKD, nondialysis CKD patients; PEG, polyethylene glycol; SC, subcutaneous.

CKD-Related Mineral and Bone Disorder

- Desired outcomes for management of disorders of mineral and bone metabolism (CKD-MBD) are to “normalize” the biochemical parameters and prevent bone manifestations, cardiovascular and extravascular calcification, and the associated morbidity and mortality.
- The KDIGO-recommended targets for calcium, phosphorus, and PTH and frequency of monitoring based on the CKD category are given in **Table 75-4**.
- Recent guidelines emphasize avoiding hypercalcemia based on evidence linking higher calcium levels with mortality and nonfatal cardiovascular events. The change in the phosphorus recommendation from maintaining levels in the normal range to “toward the normal” is based on evidence linking both high- and low-phosphate concentrations with increased mortality.
- Calcium-phosphorus homeostasis is mediated through a complex interplay of hormones and their effects on bone, the gastrointestinal (GI) tract, kidneys, and the parathyroid gland. As kidney function declines, phosphate elimination decreases resulting in hyperphosphatemia and a decrease in serum calcium concentration. Hypocalcemia stimulates secretion of PTH. As kidney function declines, serum calcium balance can be maintained only at the expense of increased bone resorption, leading to alterations in structural integrity of bone and other consequences.

TABLE 75-4

KDIGO Monitoring and Goals for Calcium, Phosphorus, and Parathyroid Hormone

	Chronic Kidney Disease Stage			
Parameter	**3**	**4**	**5**	**ESRD**
Calcium[a]				
Monitoring frequency[b] Goal	Every 6–12 months Avoid hypercalcemia [2C]	Every 3–6 months Avoid hypercalcemia [2C]	Every 1–3 months Avoid hypercalcemia [2C]	Every 1–3 months Avoid hypercalcemia [2C]
Phosphorus				
Monitoring frequency[b] Goal	Every 6–12 months Toward the normal range [2C]	Every 3–6 months Toward the normal range [2C]	Every 1–3 months Toward the normal range [2C]	Every 1–3 months Toward the normal range [2C]
Intact PTH				
Monitoring frequency[b] Goal	Based on baseline level and CKD progression Avoid progressively rising levels or levels persistently above the upper limit of normal [2C]	Every 6–12 months Avoid progressively rising levels or levels persistently above the upper limit of normal [2C]	Every 3–6 months Avoid progressively rising levels or levels persistently above the upper limit of normal [2C]	Every 3–6 months 2–9 times the upper normal limit [2C]

[a]Usually corrected for albumin.

[b]Not graded.

See Table 75-1 for definitions of evidence grading in brackets.

Treatment

- Dietary phosphorus restriction, dialysis, and parathyroidectomy are nonpharmacologic approaches to management of hyperphosphatemia and CKD-MBD.

Phosphate-Binding Agents

- Oral calcium compounds bind phosphate therefore decreasing phosphorus absorption from the gut and are first-line agents for controlling both serum phosphorus and calcium concentrations (**Table 75-5**). **Calcium carbonate** and **calcium acetate** are the primary preparations used. **Sevelamer** is a nonabsorbable, nonelemental hydrogel that effectively lowers phosphorus and also lowers LDL and increases HDL.
- **Lanthanum carbonate** controls phosphorus and maintains PTH in the target range with less risk of hypercalcemia than calcium-containing

binding agents. **Ferric citrate** and **sucroferric oxyhydroxide** are iron-based phosphate-binding agents.

- Adverse effects of all phosphate binders are generally limited to GI effects, including constipation, diarrhea, nausea, vomiting, and abdominal pain. Risk of hypercalcemia may necessitate restriction of calcium-containing binder use and/or reduction in dietary intake. Aluminum and magnesium binders are not recommended for regular use in CKD because aluminum binders have been associated with CNS toxicity and the worsening of anemia, whereas magnesium binders may lead to hypermagnesemia and hyperkalemia. The potential for iron overload should be considered with ferric citrate.

TABLE 75-5

Phosphate-Binding Agents for Treatment of Hyperphosphatemia in Chronic Kidney Disease Patients

Category	Drug	Brand Name	Compound Content	Starting Doses	Dose Titration[a]	Comments[b]
Calcium-based binders	Calcium acetate (25% elemental calcium)	PhosLo	25% elemental calcium (169 mg elemental calcium per 667 mg capsule)	1334 mg three times a day with meals	Increase or decrease by 667 mg per meal (169 mg elemental calcium)	Comparable efficacy to calcium carbonate with lower dose of elemental calcium Approximately 45 mg phosphorus bound per 1 g calcium acetate Evaluate for drug interactions with calcium
	Calcium carbonate[c]	Tums, Os-Cal, Caltrate	40% elemental calcium	0.5–1 g (elemental calcium) three times a day with meals	Increase or decrease by 500 mg per meal (200 mg elemental calcium)	Dissolution characteristics and phosphate binding may vary from product to product Approximately 39 mg phosphorus bound per 1 g calcium carbonate Evaluate for drug interactions with calcium
Iron-based binders	Ferric citrate	Auryxia	210 mg tablets (= 1 g ferric citrate)	420 mg ferric iron three times daily with meals	Increase or decrease dose by 1 or 2 tablets per meal	May increase serum iron, ferritin, and TSat May cause discolored (dark) stools Evaluate for drug interactions with iron
	Sucroferric oxyhydroxide	Velphoro	500 mg chewable tablets	500 mg three times daily with meals	Increase or decrease by 500 mg per day	May cause discolored (dark) stools Evaluate for drug interactions with iron
Resin binders	Sevelamer carbonate	Renvela	800 mg tablet 0.8 and 2.4 g powder for oral suspension	800–1600 mg three times a day with meals (once-daily dosing also effective)	Increase or decrease by 800 mg per meal	Also lowers low-density lipoprotein cholesterol Consider in patients at risk for extraskeletal calcification Risk of metabolic acidosis with sevelamer hydrochloride (less

						risk with carbonate formulation)
	Sevelamer hydrochloride	Renagel	400 and 800 mg tablets	800–1600 mg three times a day with meals	Increase or decrease by 800 mg per meal	May interact with cipro and mycophenolate mofetil
Other elemental binders	Lanthanum carbonate	Fosrenol	500, 750, and 1000 mg chewable tablets 750 and 1000 mg oral powder	1500 mg daily in divided doses with meals	Increase or decrease by 750 mg/day	Potential for accumulation of lanthanum due to some GI absorption (long-term consequences unknown) Evaluate for drug interactions (eg, cationic antacids, quinolone antibiotics)
	Aluminum hydroxide	AlternaGel	Content varies (range 100–600 mg/unit)	300–600 mg three times a day with meals	Not for long-term use requiring titration	Not a first-line agent; risk of aluminum toxicity; do not use concurrently with citrate-containing products Reserve for short-term use (4 weeks) in patients with hyperphosphatemia not responding to other binders Evaluate for drug interactions

[a]Based on phosphorus levels, titrate every 2–3 weeks until phosphorus goal is reached.

[b]GI side effects are possible with all agents (eg, nausea, vomiting, abdominal pain, diarrhea, or constipation).

[c]Multiple preparations available that are not listed.

TSat, transferrin saturation.

Vitamin D Therapy

- **Calcitriol**, 1,25-dihydroxyvitamin D_3, and vitamin D analogs directly inhibit or suppress PTH synthesis and also stimulate absorption of serum calcium by intestinal cells, which decreases PTH secretion by the parathyroid glands.
- Serum calcium and phosphorus should be within the normal range before initiation and during continued vitamin D therapy. Adjust vitamin D dose every 2–4 weeks based on PTH concentrations and trends in calcium and phosphorus (**Table 75-6**).
- KDIGO does not advocate for routine use of calcitriol and vitamin D analogs in the nondialysis CKD population and suggests that they be reserved for patients with CKD stages 4–5.
- The newer vitamin D analogs **paricalcitol** and **doxercalciferol** may be associated with less hypercalcemia and hyperphosphatemia. Observational studies show all-cause and cardiovascular survival benefit with these agents.

TABLE 75-6

Vitamin D Agents

Generic Name	Brand Name	Form of	Dosage Forms	Initial Dose	Dosage Range	Frequency of Dosing or Dose Titration[a]

		Vitamin D				
Nutritional vitamin D						
Ergocalciferol	Drisdol	D_2	po	Varies based on 25(OH)D levels	400–50,000 international units	Daily (doses of 400–2000 international units)
Cholecalciferol[b]	Generic	D_3	po			Weekly or monthly for higher doses (50,000 international units)
Calcifediol	Rayaldee	D_3	po	30 mcg daily	30–60 mcg	Increase after 3 months if PTH above desired range
Vitamin D and analogs						
Generic Name	**Brand Name**	**Form of Vitamin D**	**Dosage Forms**	**Initial Dose[c,d]**	**Dosage Range**	**Dose Titration[a]**
Calcitriol	Rocaltrol	D_3	po	0.25 mcg daily (varying doses administered three times per week are also used)	0.25–5 mcg	Increase by 0.25 mcg/day at 4–8 week intervals
	Calcijex		IV	1–2 mcg three times per week	0.5–5 mcg	Increase by 0.5–1 mcg at 2–4 week intervals
Doxercalciferol[e]	Hectorol	D_2	po	ND-CKD: 1 mcg daily	5–20 mcg	Increase by 0.5 mcg at 2-week intervals for daily dosing or by 2.5 mcg at 8-week intervals for three times per week dosing
				ESRD: 10 mcg three times per week		
			IV	ESRD: 4 mcg three times per week	2–8 mcg	Increase by 1–2 mcg at 8-week intervals
Paricalcitol	Zemplar	D_2	po	ND-CKD: 1 mcg daily or 2 mcg three times per week if PTH ≤500 pg/mL(ng/L; 54 pmol/L); 2 mcg daily or 4 mcg three times per week if PTH >500 pg/mL (ng/L; 54 pmol/L)	1–4 mcg	Increase by 1 mcg (for daily dosing) or 2 mcg (for three times per week dosing) at 2–4 week intervals
			IV	ESRD: 0.04–1 mcg three times per week	2.5–15 mcg	Increase by 2–4 mcg at 2–4 week intervals

[a]Based on PTH, calcium, and phosphorus levels. Decreases in dose are necessary if PTH is oversuppressed and/or if calcium and phosphorus are elevated.

[b]Multiple preparations are available that are not listed.

[c]Dose ratios are as follows: 1:1 for IV paricalcitol to oral doxercalciferol, 1.5:1 for IV paricalcitol to IV doxercalciferol, and 1:1 for IV to oral calcitriol.

[d]Daily oral dosing most common for nonhemodialysis CKD patients, IV or PO dosing three times per week more often used in the hemodialysis population.

[e]Prodrug that requires activation by the liver.

ESRD, end-stage renal disease; ND-CKD, nondialysis chronic kidney disease; PTH, parathyroid hormone.

Calcimimetics

- **Cinacalcet** and **etelcalcetide** reduce PTH secretion by increasing the sensitivity of the calcium-sensing receptor. The most common adverse events include nausea and vomiting.
- Since these agents lower serum calcium they should not be started if the serum calcium is less than the lower limit of normal. Start cinacalcet at 30 mg daily, which can be titrated to the desired PTH and calcium concentrations every 2–4 weeks to a maximum of 180 mg daily. Initiate etelcalcetide at 5 mg IV three times per week at the end of hemodialysis.

CARDIOVACULAR COMPLICATIONS OF CKD

Cardiovascular Disease

- CKD patients are at increased risk of CVD, independent of the etiology of their kidney disease and this is associated with much higher mortality rates. Traditional risk factors include diabetes, dyslipidemia, hypertension, smoking, and obesity. Nontraditional risk factors include proteinuria, hyperhomocysteinemia, anemia, inflammation, and abnormal calcium and phosphate metabolism, resulting in vascular calcification oxidative stress.
- CKD patients benefit from treatment of traditional risk factors. Aspirin is recommended for secondary prevention in all patients based on decreased mortality in observational studies.

Hyperlipidemia

- CKD with or without nephrotic syndrome is frequently accompanied by abnormalities in lipoprotein metabolism.
- KDIGO Lipid Guidelines recommend:
  1. Complete a fasting lipid profile in all adults with newly identified CKD.
  2. **Statin** treatment in adults ages 18–49 years with CKD but not treated with chronic dialysis or kidney transplantation, who have one or more of the following: known coronary disease; diabetes mellitus; prior ischemic stroke; estimated 10-year incidence of coronary death or nonfatal MI greater than 10%.
  3. Statin or statin/**ezetimibe** combination in adults >50 years with eGFR <60 mL/min/1.73 m^2 but not treated with chronic dialysis or kidney transplantation.
  4. Do not initiate statins or statin/ezetimibe combination therapy in adults with dialysis-dependent CKD. Continue these agents if patient is already taking them at the time of dialysis initiation.

See Chapter 61, Chronic Kidney Disease, authored by Joanna Q. Hudson, Lori D. Wazny, and Paul Komenda, for a more detailed discussion of this topic.