Pharmacologic Management of Chronic Kidney Disease (CKD)

CKD is defined as the presence of "abnormalities in kidney structures" (i.e., kidney damage) or "decreased kidney function" for 3 or more months. AKI is defined as abnormalities in kidney structure and function present for less than 3 months.

- abnormalities in kidney structures → detected as urinary albumin excretion rate ≥ 30 mg/day.
- decreased kidney function is detected as eGFR (or CrCl) < 60 ml/min.

Stages of CKD

- Classification of CKD with eGFR (G stages) and albuminuria (A stages) provides risk stratification for progression, complications, and treatment strategies.

Chronic kidney disease classification based upon glomerular filtration rate and albuminuria

GFR stages	GFR (mL/min/1.73 m^2)	Terms
G1	≥90	Normal or high
G2	60 to 89	Mildly decreased
G3a	45 to 59	Mildly to moderately decreased
G3b	30 to 44	Moderately to severely decreased
G4	15 to 29	Severely decreased
G5	<15	Kidney failure (add D if treated by dialysis)
Albuminuria stages	**AER (mg/day)**	**Terms**
A1	<30	Normal to mildly increased (may be subdivided for risk prediction)
A2	30 to 300	Moderately increased
A3	>300	Severely increased (may be subdivided into nephrotic and nonnephrotic for differential diagnosis, management, and risk prediction)

The cause of CKD is also included in the KDIGO revised classification but is not included in this table.

GFR: glomerular filtration rate; AER: albumin excretion rate; CKD: chronic kidney disease; KDIGO: Kidney Disease Improving Global Outcomes.

General Management of Chronic Kidney Disease (CKD)

A. Treat the Reversible Causes of Kidney Failure.
B. Prevent the Progression of Kidney Disease.
C. Adjust Drug Doses According to CrCl Values.
D. Treat Complications of Kidney Disease.

A. Treat Reversible Causes of Kidney Failure

- Hypovolemia due to vomiting, diarrhea, diuretic use, or bleeding:
  Treat with fluid resuscitation using isotonic solutions (normal saline IV)
- Hypotension due to myocardial dysfunction (e.g., heart failure):
  Treat with vasopressors, such as norepinephrine (Levophed) infusion (1-30 mcg/min) to maintain a MAP > 65 mmHg (MAP = mean arterial pressure)
- Systemic Infections:
  Treat aggressively with antibiotics since endotoxins and cytokines cause vasodilation → hypoperfusion of kidneys → hypoxia → acute tubular necrosis (ATN).

B. Prevent the Progression of Kidney Disease
(NOTE: the major factor for progression of CKD is "adaptive hyperfiltration" --> glomerulosclerosis)

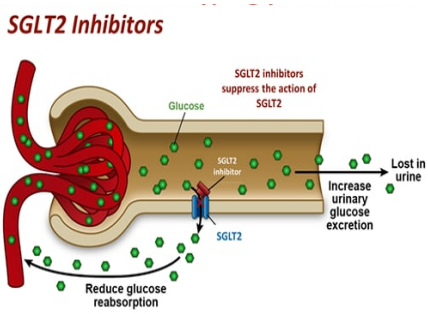
1. Maintain BP Control According to Current Guidelines
   - RAS blockers (ACEi's, ARBs) are recommended to improve renal outcomes in patients with HTN and CKD, since RAS blockers prevent adaptive hyperfiltration.
   - Monitor CKD patients on RAS blockers closely for hyperkalemia.
   - If serum creatinine levels increase more than 30% from baseline after starting ACE-I or ARB, discontinue immediately.
   - Avoid RAS blockers in patients with advanced kidney failure (stage G5)
   - Loop and thiazide diuretics are frequently used in CKD to reduce fluid retention/edema.

2. Maintain Glycemic Control to Keep HbA1C < 7 %, per ADA Guidelines

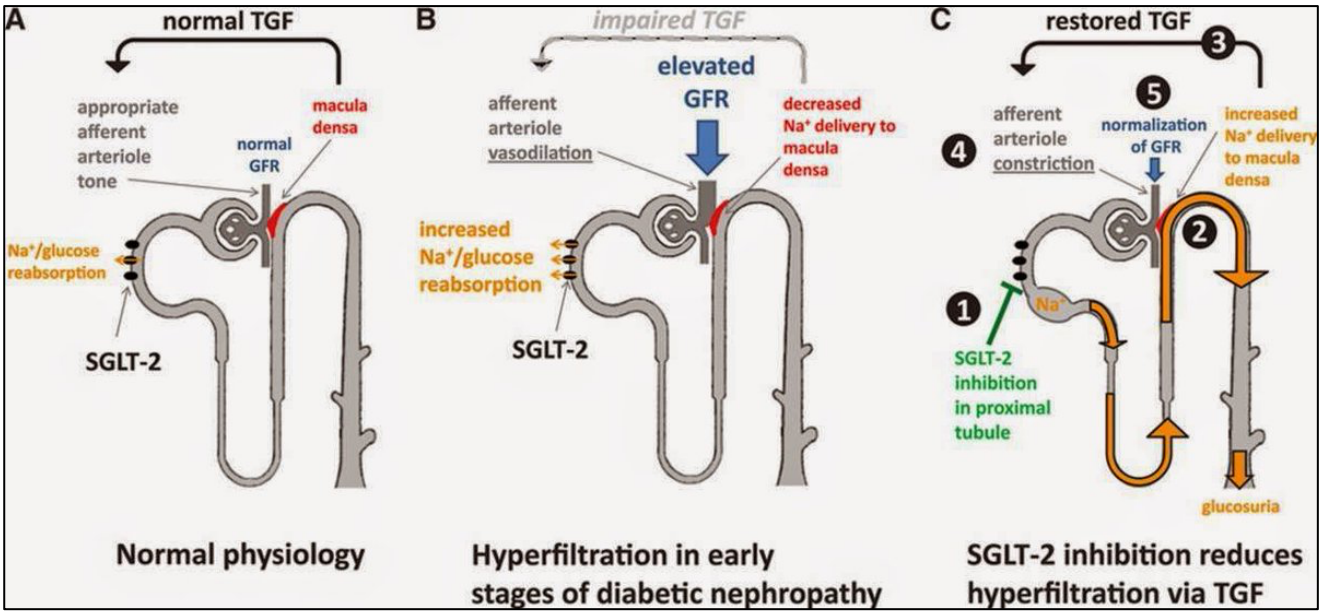
3. Use ACEi's & ARBs in Patients with Diabetic Kidney Disease (DKD) and Proteinuria

4. Use $SGLT_2$ (sodium-glucose cotransporter-2) Inhibitors

   Dapaglifozin (Forxiga) → blocks sodium and glucose reabsorption in proximal tubule → increases delivery of sodium to macula densa → constricts abnormally dilated afferent arterioles → normalizes GFR (i.e., reduces intraglomerular pressure and reduces glomerular hyperfiltration) → prevents "adaptive hyperfiltration" in CKD→ slows the progression of CKD



Tubuloglomerular Feedback (TGF)



5. Avoid nephrotoxic drugs
   - NSAIDs, glucocorticoids --> inhibit PGI --> reduce renal blood flow (GFR)
   - aminoglycosides (e.g., gentamicin), vancomycin, IV radiocontrast media (contrast-CT)

C. Adjusting Drug Doses According to Creatinine Clearance

$$CrCl\ (ml/min) = \frac{(140 - Age) \times IBW}{sCr \times 72}$$

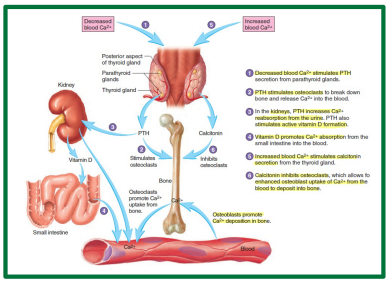
(sCr = serum creatinine level)

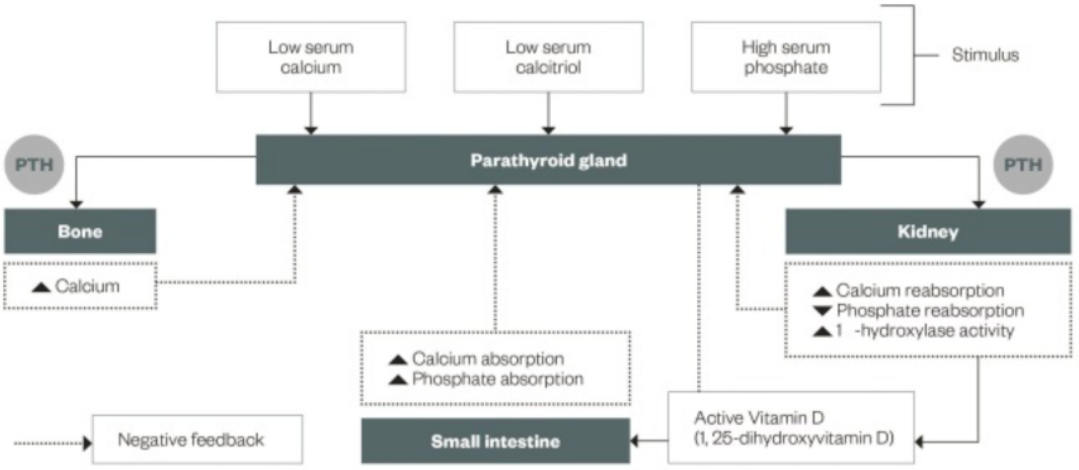
$$CrCl_{female} = CrCl \times 0.85$$

D. Treating Complications of Kidney Disease

1. CKD-MBD (Chronic Kidney Disease – Mineral and Bone Disorder)

Normal Parathyroid Regulation





Pathogenesis of CKD-MBD

- Kidneys' ability to excrete phosphate is diminished in stage 3 CKD (GFR: 30-59 ml/min)
- phosphate retention causes an increase in PTH
- elevated PTH reduces phosphate reabsorption (kidneys) and keeps serum phosphate within normal limits until kidney function declines to stage 4 (GFR: 15-29 ml/min), when kidneys' ability to excrete phosphate is limited
- serum calcitriol levels drop as GFR fall below 40 ml/min because of reduced renal calcitriol production and suppression of production by hyperphosphatemia
- lack of calcitriol leads to hypocalcemia
- hypocalcemia further stimulates PTH secretion via calcium-sensing receptors
- kidneys fail to respond to prolonged high levels of PTH
- long-term reduction of calcium (weeks-months) promotes parathyroid gland hyperplasia
- prolonged high levels PTH, known as secondary hyperparathyroidism (i.e., secondary to CKD), leads to downregulation of calcium-sensing receptors on parathyroid gland
- secondary hyperparathyroidism also leads to osteodystrophy in CKD patients
- high serum phosphate and calcium levels increases risk of coronary artery calcification

Management of CKD-MBD

Treatment of abnormal mineral homeostasis in patients with CKD includes the following:

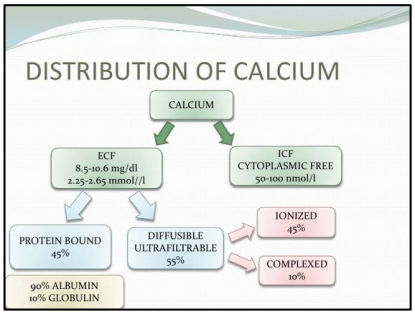
(1) Lowering high serum phosphorus levels w/phosphate binders & dietary phosphate restriction.
(2) Maintaining serum calcium levels within normal limits w/calcium supplements and calcitriol.
(3) Lowering serum PTH levels with calcitriol and vit D analogues.
Note: phosphate binders may also reduce PTH levels since hyperphosphatemia is also related to the development of secondary hyperparathyroidism.

Phosphate Binders

- Reducing phosphorus is difficult to achieve with dietary intervention alone, especially in patients with advanced kidney disease (GRF < 30 ml/min).
- Phosphate binders limit absorption from the GI tract by binding with phosphorus in meals; therefore, these agents are given with meals.
- Phosphate binders include: calcium, iron, lanthanum, aluminum, magnesium, or polymer-based agent (i.e., sevelamer).
- The choice between the use of either calcium-containing or non-calcium containing phosphate binders should be guided by serum levels of calcium and PTH, since calcium-phosphate binders in CKD with hypercalcemia is linked to coronary artery calcification.
- The main side effects of phosphate binders are GI-related: constipation, diarrhea, nausea, vomiting, and abdominal cramps.

Calcium-Containing Agents (calcium carbonate and calcium acetate)

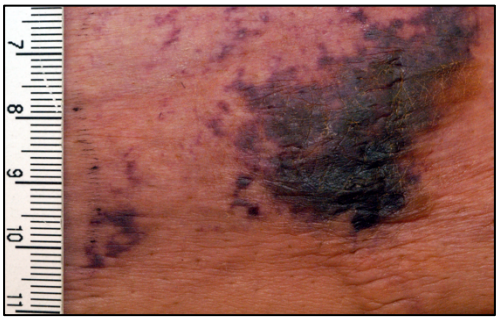
- These agents are used to correct hypocalcemia, since they may cause hypercalcemia and cardiac calcification with prolonged use.
- Calcium carbonate contains more elemental calcium and may lead to positive calcium balance and hypercalcemia than calcium acetate.
- Calcium acetate tends to increase aluminum absorption from the GI tract, therefore its use is not recommended in advanced kidney disease.
- Calcium with Vit D preparations increases risk of hypercalcemia since Vit D increases calcium absorption from the GI tract.
- Many clinicians will adjust calcium levels for low albumin. Calculating corrected calcium adjusts for the change in ratio of free (unbound) versus albumin bound calcium.



$$[\text{Calcium}]_{\text{corrected}} = [\text{Calcium}]_{\text{measured}} + \left(0.8\,(4 - [\text{albumin}])\right)$$

Correcting total serum calcium for hypoalbuminemia

- Calcium-based phosphate binders may cause calciphylaxis, calcification of the arterioles and small arteries. Calciphylaxis usually leads to necrosis of the skin and is seen in approx. 5% of dialysis patients. These patients should be switched to a non-calcium based phosphate binders like sevelamer, lanthanum carbonate, or magnesium preparation.



Aluminum Phosphate Binders

- Aluminum hydroxide (AmphoGel) is a very potent phosphorus binder indicated for short-term use (less than 4 weeks).
- In CKD, aluminum accumulates in bone and brain, causing aluminum-induced osteomalacia and encephalopathy.
- Sucralfate (Carafate), used for peptic ulcer disease, also contains aluminum and is not recommended in patients with CKD.

Agent	Availability (Pill Burden)	Comments	Adverse Effects and Warnings
Aluminum-Based Binder			
Aluminum hydroxide	320 mg/5 mL suspension	OTC	Constipation and sodium overload Aluminum toxicity: CNS, anemia, and bone disease Warnings: perforation, fecal impaction, ileus
Calcium-Based Binders			
Calcium acetate	667 mg caplets (3–12 caplets) 667 mg/5 mL (15–20 mL with meal)	Oral solution associated with higher diarrhea risk	N/V/D; hypercalcemia; vascular calcification; oral solution associated with greater diarrhea
Calcium carbonate	500–1,250 mg tablets (3–6 tablets)	OTC	N/V/D; hypercalcemia; vascular calcification

Sevelamer Hydrochloride (Renagel) / Sevelamer Carbonate (Renvela)

- Sevelamer is a non-absorbed, polymer-based agent that binds phosphorus in the GI tract without affecting serum calcium levels in patients with CKD → reduces risk of coronary calcification.
- Sevelamer lowers LDL and total serum cholesterol by binding to bile salts → reduces risk of coronary calcification / atherosclerosis.
- Sevelamer HCl is associated with lowering serum bicarbonate levels in patients on hemodialysis (HD) → increases risk of metabolic acidosis.

Resin Binders			
Sevelamer carbonate	800 mg caplet (3–12 caplets) 0.8 g/2.4 g powder packets	Reduces low-density lipoprotein cholesterol	N/V/D; hypercalcemia CI: bowel obstruction Warnings: perforation, fecal impaction
Sevelamer hydrochloride	400, 800 mg caplets 1–2 tablets TID (6–12 caplets)	Reduces low-density lipoprotein cholesterol	N/V/D; hypercalcemia CI: bowel obstruction Warnings: perforation, fecal impaction; risk of metabolic acidosis

CI, contraindications; N/V/D, nausea, vomiting, diarrhea.

Lanthanum Carbonate (Fosrenol)

- Lanthanum is a non-calcium, non-aluminum phosphate binder which dissociates into a trivalent cation with similar binding capacity as aluminum salts.
- Lanthanum has the potential to accumulate in liver, bone, and brain due to some GI absorption. Although studies have not demonstrated risks, long-term consequences remain unknown.

Magnesium Hydroxide / Magnesium Carbonate

- Magnesium agents should be used with limitations since high doses needed to bind phosphorus may cause severe diarrhea and hypermagnesemia in CKD.

Iron-Based Phos Binders: Sucroferric Oxyhydroxide (Velphoro) / Ferric Citrate (Auryxia)

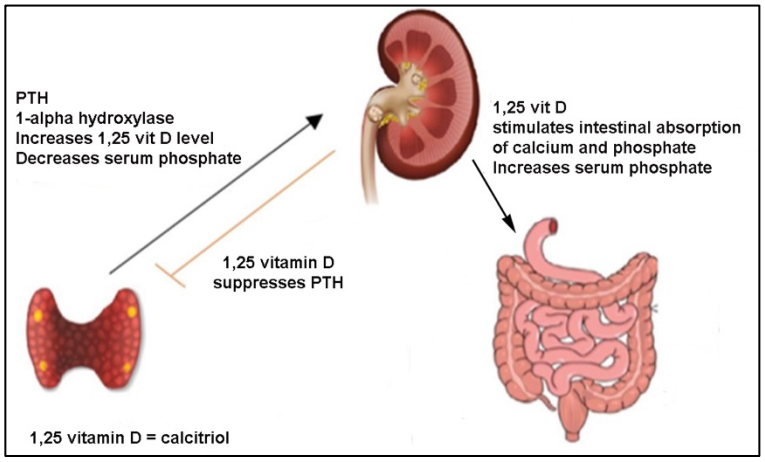
- Iron-based phosphate binders offer an advantage of supplementing iron in CKD patients with anemia.
- Side Effects: N/V/D (nausea/vomiting/diarrhea), discolored feces; risk of iron overload.

Iron-Based Agents			
Ferric citrate	210 mg ferric iron tablet (6–12 tablets)	210 mg of ferric iron = 1 g ferric citrate	N/V/D; discolored feces; iron overload Precautions: gastric/hepatic disorders; CI: hemochromatosis
Sucroferric oxyhydroxide	500 mg chewable tablet (3–6 tablets)	500 mg ferric iron = 2,500 mg sucroferric oxyhydroxide	N/D; discolored feces; iron overload Precautions: gastric/hepatic disorders; hemochromatosis
Lanthanum-Based Binder			
Lanthanum	500, 750, and 1,000 mg chewable tablets (3–6 tablets)	Chewed and crushed have similar efficacy	Accumulation in bone, brain, and liver; visible on abdominal X-ray; hypercalcemia
Magnesium hydroxide	311 mg tablets (1–6 tablets)	OTC; impair iron absorption	Hypermagnesemia; diarrhea very common
Magnesium-Based Binder			

2. Treatment of Secondary Hyperparathyroidism (SHPT)
   Vit D receptor agonists (VDRA), Vit D analogues, and calcimimetics are all considered 1st line options for lowering PTH in CKD stage 5D; and, the choice of which agent to use should be guided by serum levels of calcium, phosphate, and PTH.

   Vitamin D Receptor Agonist (VDRA): Calcitriol (Rocaltrol)

   - Calcitriol (1,25-dihydoxyvitamin D) is the active form of vitamin D synthesized in the kidney → interacts with Vit D receptors (VDR) in parathyroid, intestines, bone, and kidney.
   - As a vit D receptor agonist (VDRA), calcitriol binds to vit D receptors (VDR) on the parathyroid gland and prevents SHPT by inhibiting PTH secretion.
   - Note: Calcitriol also binds to VDR in the GI tract to stimulate absorption of calcium and phosphorus. Therefore, it is important to control serum phosphorus and calcium levels in patients with CKD-MBD before using calcitriol, since hypercalcemia and elevated phosphorus levels may be detrimental to vascular tissue.



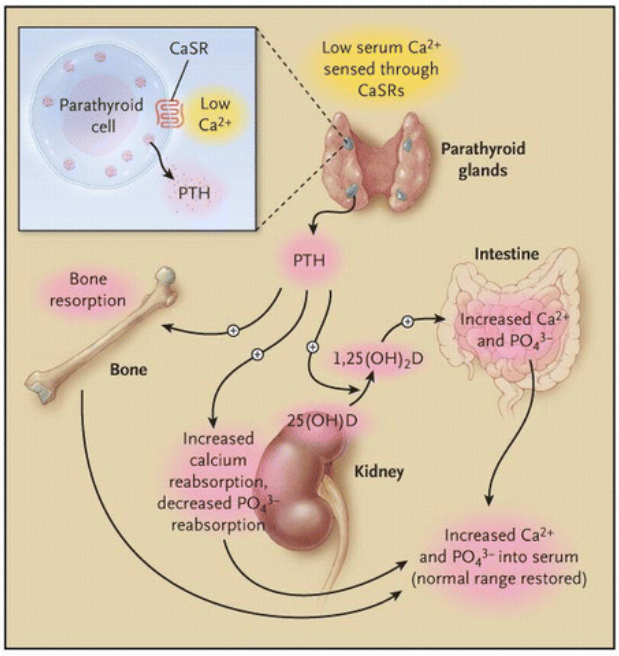
   - Calcitriol is available as an oral formulation (Rocaltrol) or IV formulation (Calcijex) with usual doses of 0.25-0.5 mcg/day.

Vitamin D Analog: Paricalcitol (Zemplar)

- Paricalcitol significantly decreases PTH by selectively binding to VDR in the parathyroid gland while decreasing the potential for hypercalcemia with calcitriol.
- Paricalcitol is approx. 10 times less hypercalcemic and hyperphosphatemic than calcitriol.
- Paricalcitol is available IV (0.4-1 mcg/kg IV with each dialysis) or PO (1-4 mcg PO daily or TIW).

Calcimimetics: Cinacalcet (Sensipar)

- Cinacalcet is a calcimimetic agent that increases sensitivity of the calcium-sensing receptors (CaSR) in the parathyroid gland to calcium → inhibiting release of PTH
- Cinacalcet may be offered as an additional agent to lower PTH when Vit D cannot be increased because of elevated calcium or phosphorus levels.
- Cinacalcet is only approved for use in CKD patients on dialysis because it is associated with frequent hypocalcemic episodes; however, it is an emerging option in treatment of secondary hyperparathyroidism (SHPT) in pre-dialysis patients with CKD.
- Cinacalcet is initially dosed at 30 mg PO daily, titrated upwards according to response.
- Hypocalcemia is the main side effect associated with cinacalcet and thus regular monitoring of serum calcium and phosphate levels is indicated.

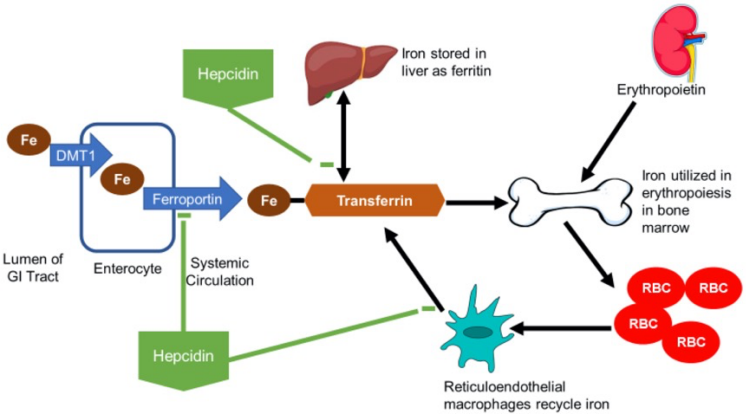


Parathyroidectomy

- The parathyroid glands enlarge as a compensatory response to hyperphosphatemia, hypocalcemia, and low calcitriol levels in patients with CKD.
- Parathyroidectomy, subtotal or total, is reserved for patients with severe hyperparathyroidism with PTH levels greater than 1,000 pg/ml (normal PTH = 10-55 pg/ml), concomittant hypercalcemia, and failure to respond to pharmacologic therapy.
- Timely intervention with Vit D therapy is crucial to prevent parathyroid hyperplasia, since Vit D cannot reverse parthyroid hyperplasia.
- Hypocalcemia is permanent in total parathyroidectomy, therefore long-term treatment with calcitriol and oral calcium supplements is necessary.

3. Anemia in Chronic Kidney Disease

- Anemia arises from multiple pathophysiological factors, including the presence of inflammation, elevated levels of hepcidin, and an impaired ability of the peritubular interstitial cells to produce erythropoeitin (EPO). As renal mass declines (measured by declining GFR), so does production of EPO.
- Ferroportin is the transporter for iron absorption into the systemic circulation. Transferrin binds free iron (ferritin) to transport it to the liver for storage and bone marrow for Hgb production. Hepcidin, produced by the liver, regulates iron release from stores in liver and reticuloendothelial macrophages. Hepcidin binds to ferroportin, preventing iron absorption and preventing iron utilization from stores to prevent iron overload. However, in CKD, hepcidin is increased due to decreased renal elimination and inflammation, leading to decreased iron absorption from the GI tract and decreased iron release from macrophage and hepatocyte stores.



Iron Therapy

- Iron supplementation is required in absolute iron deficiency and can be given oral or IV.
- Oral bioavailability of iron is poor (10-15%) and medications that reduce gastric pH (e.g., PPIs, H_2RAs) reduce iron absroption.
- Iron is absorbed best on an empty stomach.
- Ascorbic acid may be given with oral iron to increase bioavailability.
- Ferrous Sulfate 325 mg (65 mg elemental iron) PO TID is the initial therapy used in CKD.
- In CKD, serum ferritin below 100-200 ng/ml or iron saturation less than 20% is suggestive of iron deficiency (Note: TSAT = transferrin saturation = capacity of transferrin to bind to iron). .
- Kidney Disease Improving Global Outcomes (KDIGO) recommends initiating iron supplementation in adults if transferrin saturation (TSAT) is $\leq$ 30% and ferritin is $\leq$ 500 ng/ml.
- Iron stores should be repleted with oral or IV iron prior to starting an erythropoiesis stimulating agents (ESA).

Intravenous Iron

- IV iron is the prefered route of administration in patients who have failed a 3-6 month trial of oral iron.
- Side effects of IV iron include: flushing, headache, hypotension, anaphylaxis.
- Anaphylaxis is most concerning with dextran formulations (Infed).
    - Non-dextran forms have a low risk of anaphylaxis, with iron sucrose (Venofer) being the lowest.

Table 3. Treatment Options for Anemia of CKD

IV Iron Therapies	
Iron dextran	One-time test dose 25 mg IV 100 mg IV or IM daily for 10 doses OR 250-100 mg slow IV infusion Alternatively: dose (mL) = 0.0442 (desired Hgb–observed Hgb) × LBW + (0.26 × LBW)
Iron sucrose	200 mg IV × 5 doses in 14 days OR 500 mg slow IV infusion on days 1 and 14 OR 300 mg, 300 mg, 400 mg IV infusion, all 14 days apa
Sodium ferric gluconate	250 mg slow IV infusion[a]
Ferumoxytol	510 mg IV × 2 doses 3-8 days apart

Erythropoiesis Stimulating Agents (ESAs)

- Chronic anemia in CKD → chronic myocardial hypoxia → left ventricular hypertrophy (CHF)

- Given the cardiovascular risks, KDIGO guidelines recommend intiating ESA when hemoglobin (Hgb) is below 9 g/dL and targeting treatment to 10-11 g/dL. Higher Hgb levels increases the risk of stroke and other cardiovascular events.

    - Epoetin (Epogen/Procrit): 50 UNITS/kg (3000-4000 UNITS/dose) SC or IV once or twice weekly.
    - Darbepoetin (Aranesp): 0.45 mcg/kg SC or IV every 2-4 weeks.
    - NOTE: SC dosing of erthyropeietin is 30% more effective than IV dosing.

- ESA Side Effects: hypertension (20%), headache, and hypersensitivity reactions.

- Goal of administrating ESA is to reduce the risk of blood transfusion, which imparts negative consequences for subsequent transplantation due to allosensitization.

ESA Therapies	
Darbepoetin alfa	Initial: 0.45 mcg/kg IV or SC every 4 wk
Epoetin alfa	Initial: 50-100 U/kg IV or SC 3 times/wk

Summary: Complications of Chronic Kidney Disease (CKD)