Anemia

- The current FDA labeling for all ESAs wans that dosing ESAs to target Hb levels > 11 g/dL for CKD patients increases the risk for death, serious CV reactions, and stroke.
- Non-pharmacologic therapy for anemia of CKD includes maintaining adequate dietary intake of iron as well as folate and B_{12}.

Anemia: Iron Supplementation

- Iron supplementation is first-line therapy for anemia of CKD if iron deficiency is present, and for some patients the target Hb may achieved without concomitant ESA therapy.
- **Oral iron formulations:**
  - Ferrous salts: ferrous sulfate (elemental iron 20%), ferrous gluconate (12%), ferrous fumarate (33%)
  - iron polysaccharide (100%)
  - carbonyl iron (100%)
  - Ferric maltol: non-salt formulation that contains iron in a stable ferric state
  - Heme iron polypeptide formulation (elemental iron 12 mg)
- ~ 10% of orally administered iron is absorbed in the duodenum and upper jejunum

Anemia: Iron Supplementation

- Absorption of iron is decreased by food and achlorhydria.
- Some oral iron formulations also include ascorbic acid to enhance iron absorption.
- Soluble ferric pyrophosphate citrate (Triferic) is an iron compound added to the dialysate used for HD and crosses from the dialysate to the blood side of the dialyzer by diffusion to allow for continuous iron administration during the procedure.
  - Ferric pyrophosphate binds directly to transferrin, bypassing the reticuloendothelial system, and is delivered to the bone marrow for use in RBC production.
  - But it no significant increase in ferritin or in non-transferrin bound iron

Anemia: Iron Supplementation

- **IV Iron Preparations:**
- They are colloids that consist of an iron-containing core that is surrounded by a carbohydrate shell to stabilize the iron complex.
- Available agents differ in the size of the core and the composition of the surrounding carbohydrate.
- The differences affect the rate of dissociation of iron from the complex, the rate of distribution and the maximum tolerated dose and rate of infusion.

Anemia: Iron Supplementation

- IV Iron Preparations:
  - Ferric carboxymaltose
  - Ferrumoxytol
  - Iron dextran
  - Iron sucrose
  - Sodium ferric gluconate
- Parenteral iron improves the responsiveness to ESA therapy and lower ESA doses can be used to maintain the target Hb in HD patients.
- Adverse effects of oral iron are primarily GI and include constipation, nausea and abdominal cramping.
- Adverse effects of IV iron include allergic reactions esp anaphylaxis, hypotension, dizziness, dyspnea, headaches, lower back pain, arthralgia, syncope and arthritis.

Anemia: Iron Supplementation

- Serious reactions to iron dextran including respiratory complications (anaphylactic-type reactions including fatalities) and CV collapse have been reported.
- Anaphylaxis risk in patients newly exposed to IV iron products (dextran, gluconate, sucrose or ferumoxytol) reported the highest risk with iron dextran and the lowest risk with iron sucrose.
- Long-term administration of IV iron also introduces a risk of iron overload which may affect several organ systems, leading to hepatic pancreatic and cardiac dysfunction.
- Maintaining target serum ferritin and Tsat values is the most reasonable approach to minimize the risk of iron toxicity.

Anemia: Iron Supplementation

- If symptomatic overload does occur, iron chelating agents may be necessary:
  - Deferoxamine (Desferal®)
  - Deferiprone (Ferriprox®)
  - Deferasirox (Exjade®)
  - Phlebotomy
- Iron absorption is decreased by other elements (e.g. calcium in calcium-containing phosphate binders), medications that increase the pH of the GI tract such as proton pump inhibitors and H2-antagonists, and antibiotics including doxycycline, tetracycline and fluoroquinolones.

Anemia: ESA

- Erythropoiesis-Stimulating Agents
  - Epoetin alfa (Espogen®, Renogen®, Eporon®, Eprex®, Hemax®)
  - Epoetin alfa-epbx (Retacrit®)
  - Epoetin beta (Recormon®)
  - Darbepoetin alfa (NESP®)
  - Methoxy PEG epoetin beta (Mircera®)
- Epoetin alfa
  - A glycoprotein manufactured by recombinant DNA technology that has the same amino acid sequence as endogenous erythropoietin
- Darbepoetin alfa
  - Has 2 additional N-linked carbohydrate chains that decrease the affinity for the erythropoietin receptor, but yield a longer duration of activity

Anemia: ESA

- Methoxy PEG-epoetin beta
  - Created by integrating an amide bond between methoxy PEG-butanoic acid and either the N-terminal or ε-amino group of lysine present in epoetin beta
  - Has much longer half-life than the others
- All available ESAs may be administered by either the IV or the SC route
- With initiation of ESA therapy or a change in dose, the Hb may begin to rise approximately 10 days. The Hb continues to increase until the life span of the cells stimulated by ESA therapy is reached (mean 2 mo; range 1-4 mo in patients with ESRD)

Anemia: ESA

Drug	Starting Dose	Half-life (hrs)
Epoetin alfa, -epbx	Adult: 50-100 units/kg 3TW Ped: 50 units/kg 3TW	IV: 8.5 SC: 24
Darbepoetin alfa	No-CKD: 0.45 mcg/kg Q4W CKD 5 & Ped : 0.45 mcg/kg Q1W or 0.75 mcg/kg Q2W	IV: 25 SC: 48
Methoxy PEG-epoetin beta	CKD: 0.6 mcg/kg Q2W; Once Hb stabilizes, double dose and administer monthly	IV: 134 SC: 139

Anemia: ESA

- The most common causes of resistance are iron deficiency, folate and vitamin B_{12} deficiency, acute illness, inflammation, infection, chronic bleeding, aluminum toxicity, malnutrition, hyperparathyroidism, cancer and chemotherapy.
- Use of ACEIs and ARBs has also been associated with hypo-responsiveness to ESA therapy.
- Hypertension is the most common adverse event reported with ESAs and may be associated with the rate of rise in Hb.
- The potential for adverse effects calls for close monitoring of the rate of rise in Hb, changes in BP and neurologic symptoms following initiation of therapy or a change in ESA dose.

Anemia: ESA

- Antibody-associated pure red cell aplasia (PRCA) caused by induction of antibodies directed against the ESA molecule was primarily associated with SC administration of epoetin alfa (Eprex®) and PEG-epoetin beta.
- An evaluation for PRCA should be considered for patients receiving ESA therapy for more than 8 weeks who develop either a rapid decrease in Hb level or require 1-2 blood transfusions per week and have an absolute reticulocyte count of < 10,000/uL with a normal platelet and WBC count.
- Discontinuation of ESA therapy is recommended if antibody-mediated PRCA develops because Ab are cross-reactive and continued exposure may lead to anaphylactic reaction.

CKD-MBD

- Management of PTH, phosphorus and calcium is important in preventing CKD-MBD and CV and extravascular calcifications.
- KDIGO monitoring and goals for calcium, phosphorus and PTH (6-12 mo, 3-6 mo, 1-3 mo)
- KDIGO recommends that PTH values for ESRD patients be within 2-9 x the upper limit of the normal range (= 130-600 pg/mmL)

CKD-MBD

- **Dietary phosphorus restriction**
  - is a first-line intervention for management of hyperphosphatemia and should be initiated from most patients with CKD3-5.
  - Dietary restriction of phosphorus in providing enough protein to prevent malnutrition.
  - Inorganic sources: frozen meals, preservatives or additives used during food processing
  - Organic sources: meat and plant
- **Dialysis**
  - HD and PD lower serum phosphorus and calcium
  - It is recommended that the dialysate calcium concentration be between 2.5 and 3 mEq/L
  - Conventional dialysis alone does not usually control hyperphosphatemia

CKD-MBD

- **Parathyroidectomy**
  - A therapeutic option for patients with persistently elevated PTH associated with hypercalcemia and/or hyperphosphatemia who are refractory to medical therapy
  - Postoperative hypocalcemia, hypophosphatemia and hypomagnesemia may occur because of a marked increase in bone production in relation to bone absorption ("hungry bone syndrome").
  - Treatment with supplemental calcium and vitamin D may be required for weeks or months.
  - For some patients a parathyroidectomy may be ineffective and there is also the risk of over-suppression of PTH and prolonged hypocalcemia.

CKD-MBD

- **Phosphate-Binding Agents**
  - They are used in addition to dietary phosphorus restriction to limit GI absorption and indicated for CKD patients with progressive or persistent hyperphosphatemia.
  - Must be taken these agents with meals to maximize the binding of phosphorus from dietary sources and are excreted in feces.
  - Calcium compounds are well established as first-line agents for control of serum phosphorus. Calcium citrate is not used due to increasing Al absorption and causing more GI side effects.
  - Acid-suppressing agents such as ranitidine and PPIs may reduce the phosphate-binding activity.

Phosphate-Binding Agents

Category	Drug	Starting Doses
Calcium-based	Calcium acetate (25% elemental Ca)	1,334 mg TID with meals Note: 1 gm Ca acetate bound P ~45 mg
	Calcium carbonate	500 -1000 mg (elemental Ca) TID with meals
Iron-based	Ferric citrate	420 mg ferric iron TID with meals Note: may increase iron, ferritin and Tsat
	Sucroferric oxyhydroxide	500 mg chew TID with meals
Resin	Sevelamer carbonate (Renvela®) Sevelamer HCl (Renagel®)	800-1600 mg TID with meals Note: once-daily dosing also effective, also lower LDL, risk of metabolic acidosis, may interact with FQs and MPM
Other elemental	Lanthanum carbonate (Fosrenol®)	1,500 mg chew in divided doses with meals
	Aluminum hydroxide	300-600 mg TID with meals Note: Not a first-line agent; risk of Al toxicity

CKD-MBD

- **Phosphate-Binding Agents**
  - *Sevelamer* is approved for ESRD patients that effectively lowers phosphorus and has also been shown to lower LDL and increase HDL cholesterol.
  - *Lanthanum carbonate* is approved for patients with ESRD and has efficacy in controlling phosphorus and maintaining PTH in the target range with less risk of hypercalcemia than calcium-containing binders.
  - *Ferric citrate and sucroferric oxyhydroxide* are the newest agents approved for ESRD patients.
  - KDIGO recommends avoiding the long-term use of aluminum containing binders in all patients with CKD stage 3a-5D.
  - Magnesium-containing antacids are also effective phosphate binders; however, their use is limited by the frequent occurrence of GI side effects (diarrhea) and the potential for Mg accumulation.

CKD-MBD

- **Phosphate-Binding Agents**
  - Adverse effects of all available phosphate binders are generally limited to constipation, diarrhea, nausea, vomiting and abdominal pain.
  - Aluminum binders have been associated with CNS toxicity and worsening of anemia.
  - Magnesium binder use may lead to hypermagnesemia and hyperkalemia.
  - The potential for iron overload should also be considered with ferric citrate, given the effects on increasing iron indices.

CKD-MBD; Vitamin D Therapy

Nutritional Vit D	Form	Initial Dose	Dosage Range
Ergocalciferol	D_2	Based on 25(OH)D levels	400-50,000 IU
Cholecalciferol	D_3		50,000 IU Q1W or Q1M
Calcifediol	D_3	30 mcg daily	30-60 mcg
Vit D and Analogs	**Form**	**Initial Dose**	**Dosage Range**
Calcitriol (Rcaltrol®)	D_3	0.25 mcg daily	0.25-5 mcg
Doxercalciferol	D_2	ND-CKD: 1 mcg daily ESRD: 10 mcg TIW	5-20 mcg
Paricalcitol	D_2	PTH ≤ 500 pg/mL: 1 mcg daily or 2 mcg TIW PTH > 500 pg/mL: 2 mcg daily or 4 mcg TIW	1-4 mcg

CKD-MBD

- **Vitamin D Therapy**
  - Vitamin D is a cholesterol derivative and is transported in the circulation by vitamin D-binding protein.
  - Endogenously synthesized D_3 and NVD compounds (D_2 or D_3) are converted in the liver to 25(OH)D by the 25-hydroxylase enzyme. The 25(OH)D form is converted to the active form 1,25-dihydroxyvitamin D (either D_2 or D_3 based on parent compound) by the 1-α-hydroxylase enzyme.
  - The concentration of 25(OH)D is most commonly measured to diagnose vitamin D deficiency.

CKD-MBD

- **Vitamin D Therapy**
  - *Calcitriol* and the vitamin D analogs bind to the vitamin D receptors (VDRs), which are located in many organ systems including the parathyroid glands, intestine, bone, kidney, heart, nervous, and immune systems.
  - Vitamin D inhibits or suppresses PTH synthesis and also stimulates absorption of serum calcium (and phosphorus) by intestinal cells.
  - *Paricalcitol and doxercalciferol* retain activity with vitamin D receptors on the parathyroid gland to effectively lower PTH, but have less risk of hypercalcemia and hyperphosphatemia due to their lower intestinal activity.
  - Calcitriol, paricalcitol and doxercalciferol are all effective in lowering PTH in patients with CKD; however, the undesired effect is raising calcium and phosphorus concentrations due to increased intestinal absorption.

CKD-MBD

- **Vitamin D Therapy**
  - They may cause hypercalcemia and hyperphosphatemia, an effect that is most likely with calcitriol.
  - Cholestyramine may reduce the absorption of orally administered calcitriol and doxercalciferol.
  - In vitro data suggest that paricalcitol is metabolized by the hepatic enzyme CYP3A4.
  - KDIGO guidelines support administering NVD to patients CKD 3a-5 and ESRD with vitamin D deficiency or insufficiency.
  - Calcitriol, doxercalciferol or paricalcitol should be administered whn PTH remains elevated despite the achievement of adequate 25(OH)D levels.
  - Prior to starting therapy, the serum calcium and phosphorus should be within the normal range.

CKD-MBD

- **Calcimimetics**
  - *Cinacalcet HCl (Sensipar®)* and *Etelcalcetide* are approved for treatment of 2nd hyperparathyroidism in CKD patients on dialysis.
  - They work through their interactions on the calcium-sensing receptor (CSR) located on the surface of the chief cells of the parathyroid gland resulting in increased sensitivity of the receptor to extracellular calcium and subsequently reducing PTH secretion.
  - In non-dialysis CKD patients, cinacalcet reduced PTH, but was associated with a high incidence of hypocalcemia.
  - Cinacalcet may be used as a single agent; however, combined therapy with vitamin D is often necessary to achieve tart PTH, calcium and phosphorus values.
  - Etelcalcetide was a greater reduction in serum calcium and phosphorus compared with cinacalcet.

CKD-MBD

- **Calcimimetics**
  - The most frequent adverse events are nausea and vomiting.
  - They should not be started if the corrected serum calcium is < 8.4 mg/dL.
  - Potential manifestations of hypocalcemia include paresthesia, myalgia, cramping, tetany, and convulsions. Hypocalcemia may also lead to Q-T interval prolongation and ventricular arrhythmias.
  - Cinacalcet is partially metabolized by CYP3A4. It is also a potent inhibitor of CYP2D6.
  - Food has been shown to increase absorption of cinacalcet by up to 82% compared with fasting.
  - There are no interactions reported with etelcalcetide. This agent is not a substrate or inhibitor of CYP isoenzymes or transporter proteins.

CKD-MBD

- **Calcimimetics: Cinacalcet**
  - The recommended dose is 30 mg orally once daily.
  - Ca and P should be measured at 1 week and PTH should be measured within 1-4 weeks after starting or adjusting the dose.
  - The dose should be titrated every 2-4 weeks to a maximum dose of 180 mg once daily until the desired PTH values are achieved and to maintain goal serum calcium concentrations.
  - Patients with hepatic disease may require lower doses, since the cinacalcet half-life is approximately doubled in those with severe liver disease.
  - If switching from Cinacalcet to Etelcalcetide, then Cinacalcet should be discontinued for at least 7 days prior to starting Etelcalcetide.

CKD-MBD

- **Calcimimetics: Etelcalcetide**
  - It should be initiated at a dose of 5 mg administered IV TIW at the end of the hemodialysis treatment (since it is removed by HD).
  - Ca and P should be measured 1 week after initiation and then every 4 weeks for maintenance therapy.
  - PTH levels should be measured 4 weeks after initiation and then per protocol.
  - If PTH levels are above the recommended target range and the corrected serum Ca is within the normal range, the dose of Etelcalcetide should be increased in 2.5- or 5-mg increments up to a maximum dose of 15 mg.
  - In patients with a corrected Ca at ≥ 7.5 mg/dL without symptoms of hypocalcemia a decrease in dose or temporary discontinuation may also be considered.

CVD complications

- Traditional CVD risk factors in patients with CKD include DM, DLP, HTN, LVH, smoking and obesity.
- Nontraditional risk factors include proteinuria, hyperhomocysteinemia, anemia, inflammation, and abnormal Ca and P metabolism resulting in vascular calcification oxidative stress.
- These patients should also receive the standard assessments and treatments such as statins for CKD1-5 (non-dialysis), beta-blockers, ACEIs/ARRBs and antiplatelet agents.
- For patients with heart failure, the therapies should be aware that RAAS blockade (e.g. ACEI, ARB, spironolactone, eplerenone) and diuretic therapy (e.g. furosemide, metolazone) may lead to significant changes in GFR and serum potassium concentrations.
- Aspirin (ASA) is recommended for 2nd prevention in all patients with CKD based on decreased mortality in observational studies.

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Hyperlipidemia

- CKD ± nephrotic syndrome is frequently accompanied by abnormalities in lipoprotein metabolism.
- In patients with nephrotic syndrome*, the major lipid abnormalities are elevation of plasma total and LDL cholesterol, ± low HD cholesterol and elevated TG.
- *Nephrotic syndrome is a kidney disorder that causes the body to pass too much protein in urine. It is usually caused by damage to the clusters of small blood vessels in the kidney that filter waste and excess water from the blood.

Hyperlipidemia: Statins

- Statins have been shown to decrease mortality and CV events in CKD 1-5 patients.
- A meta-analysis of statins in <u>non-dialysis CKD</u> showed significant reductions in major CV events, CV death, all-cause mortality; myocardia infarction but uncertain effects on stroke
- The KDIGO lipid guidelines:
  - Suggest statin treatment in patients age 18-49 years with CKD but not treated with chronic dialysis or kidney Tx with known coronary disease (MI or coronary revascularization); DM, prior ICS; estimated 10-year incidence of coronary death or nonfatal MI > 10%.
  - Patients age > 50 years with eGFR < 60 mL/min/1.73m² but not treated with chronic dialysis or kidney Tx, recommended treat with a statin or statin/ezetimibe combination.
  - In patients with dialysis-dependent CKD, suggested that statins or statin/ezetimibe combination at the time of dialysis initiation, and suggested that these agents be continued.