ANEMIA & HEMODIALYSIS
The anemia of CKD is, in most patients, normocytic and normochromic, and is due primarily to reduced production of erythropoietin by the kidney and to shortened red cell survival.
Anemia in those with CKD should begin when the Hgb level is less than 12 g/dL in females, and Hgb levels of less than 13.5 g/dL in adult males.

Anemia becoming increasingly common as GFRs decline below 60 mL/min per 1.73 m².
Anemia is associated with:

- Independent risk factor for development of LVH
- Independent risk factor for hospitalization (CV and non-CV related)
- Increased CV morbidity and mortality
- Poorer quality of life
- Higher relative risk for death than diabetes
Anemia may be a risk factor for progression of chronic renal dysfunction to ESRD.
OVERVIEW OF TREATMENT OPTIONS

- Red blood cell transfusions

  — Among patients with CKD, red blood cell transfusions are almost universally successful in raising hemoglobin levels.
Transfusions often can ameliorate the patient's symptoms and improve health-related quality of life.

Complications include transfusion-transmitted infection, immunologic sensitization, iron overload syndromes, volume overload, and/or transfusion reactions.
Androgens

Prior to the availability of epoetin, androgens (which may increase endogenous erythropoietin production, sensitivity of erythroid progenitors to the effects of erythropoietin, and red blood cell survival) were used regularly in the treatment of anemia in dialysis patients.
Erythropoietin stimulating agents:

- The administration of these agents is particularly attractive because they practically eliminate the need for red cell transfusions, with an attendant decrease in and/or risk for transfusion-related complications.
- They also help *mobilize iron stores*, which is particularly beneficial in patients with CKD and iron overload due to previous transfusions.
EPO be given to predialysis patients with a hemoglobin concentration less than 11 g/dL.

Target Hb levels in the range of 11 to 12 g/dL among EPO treated predialysis patients with CKD.

We recommend NOT targeting Hgb levels above 13 g/dL.
EPO is recommended for use in hemodialysis patients who have a hemoglobin level of less than 11 g/dL. Better quality of life without an increase in adverse reactions are associated with Hgb values between 11 and 12 g/dL compared to values below this level.
- EPO should NOT be started until iron status has been evaluated.
- Among patients with evidence of iron deficiency, iron supplements should be given first and iron deficiency corrected prior to initiating EPO.
In addition, other causes of anemia should be excluded and hypertension should be corrected before EPO therapy is begun.
To ensure effective erythropoiesis with ongoing EPO administration, adequate iron stores must be continually maintained in both CKD and dialysis patients.

Iron therapy be administered for maintenance therapy among most patients receiving EPO.
Oral iron is often effective in predialysis patients and those on peritoneal dialysis; by comparison, most hemodialysis patients require intravenous iron.
**DIAGNOSIS OF IRON DEFICIENCY**:

The evaluation of patients with kidney disease and anemia must include red blood cell indices, reticulocyte count, serum iron, TIBC, percent transferrin saturation, serum ferritin, and testing for occult blood in stool.
Absolute and functional iron deficiency

Among hemodialysis patients, absolute iron deficiency is likely to be present when:

- The percent transferrin saturation (plasma iron divided by TIBC x 100) falls below 20 percent
- The serum ferritin concentration is less than 200 ng/mL
Functional deficiency is associated with transferrin saturation $\leq$ 20 percent and elevated ferritin level (between approximately 100 to 800 ng/mL or even higher).
For maintenance iron therapy, transferrin saturation be maintained below 50 percent and the serum ferritin level below 500 ng/mL.

Do not routinely administer intravenous iron to patients with ferritin levels above 500 ng/mL and anemia, although each patient should be individually assessed.
OVERVIEW OF DOSING REGIMENS:

Among iron-deficient hemodialysis patients, if iron indices indicate absolute or functional iron deficiency:

- 100 mg iron sucrose can be given at each consecutive hemodialysis treatment for a total of 10 doses (1000 mg in total).
Repeat the initial loading regimen if the transferrin saturation remains below 20 percent, the hemoglobin level does not increase to the target level, or the serum ferritin level remains below 200 ng/mL.
Among predialysis and peritoneal dialysis, iron is principally given orally to treat and prevent development of iron deficiency.

**IV iron** may be necessary and is typically given when iron indices fall below target levels, indicating the development of iron deficiency.
Major adverse consequences with normal or near-normal Hgb levels include cerebrovascular events, arteriovenous access thrombosis, and hypertension.
Among hemodialysis patients, suggest administering EPO intravenously rather than subcutaneously.

In general, to attain hemoglobin levels of 11 g/dL or higher, a dose increase of 25 percent would be appropriate after four weeks if initial dosing levels do not result in a rate of increase in the hemoglobin of approximately 0.3 to 0.5 g/dL per week.
Changing the dose of EPO more than once over a two- to four-week period is unnecessary in most instances.

Among those with increases in hemoglobin of greater than 2.5 to 3 g/dL per month, the EPO dose should be reduced by at least 25 percent.
Hyporesponsiveness to EPO:

- 450 U/kg per week intravenous EPO or 300 U/kg per week subcutaneous EPO, per K/DOQI.

The most common cause of resistance to EPO is absolute iron deficiency.
- Bone disease due to secondary hyperparathyroidism
- Occult malignancy and unsuspected hematologic disorders
- MM /myelofibrosis/myelodysplastic syndrome.
- Hemoglobinopathies
- The administration of ACE inhibitors and/or ARBs.
- Development of pure red cell aplasia associated with the presence of neutralizing anti-erythropoietin antibodies
- Presence of HIV infection.
Chronic inflammation: presence of a failed kidney transplant or an occult infection of an old nonfunctioning AV graft may underlie such inflammation in some patients.

Accumulation of aluminum in bone.
Side effects

The most common side effects of EPO treatment, aside from hypertension and its related problems, are headache (which occurs in 15 percent of cases) and an influenza-like syndrome (affecting 5 percent).

The influenza-like syndrome is of unknown etiology, but is responsive to anti-inflammatory drugs.
- HTN following erythropoietin:
- Approximately 20 to 30 percent of patients who receive erythropoietin iv may develop an elevation in diastolic pressure of 10 mmHg or more.
- In comparison, the BP is less likely to rise after subcutaneous administration.
PREVENTION AND TREATMENT:

- BP must be closely monitored in all patients with CKD, particularly during initiation with EPO.
- Therapy of EPO-induced hypertension begins with prevention.
- The risk of hypertension can be ameliorated by raising the hematocrit slowly.
Antiplatelet agents may reduce the risk of EPO-induced hypertension.

Why this might occur is not clear.
Patients who still become hypertensive can be treated with fluid removal (via dialysis and the administration of antihypertensive agents).
- **Beta-adrenergic blockers** and **vasodilators** should be considered as agents of first choice, although calcium channel blockers and ACE inhibitors also may be effective.
The dose of EPO should be reduced or discontinued for several weeks in severe cases or when other therapeutic measures are ineffective.
For hemodialysis patients in whom EPO administration has been initiated or the dose has recently changed, the hemoglobin should be measured once per week to adequately assess the response; by comparison, the hemoglobin of patients with stable hemoglobin levels and EPO dose can be assessed every two to four weeks.
Future Treatment Options for CKD-Related Anemia

- Continuous erythropoiesis receptor activator (CERA) – not FDA Approved
  - SC or IV dosing up to 4-week interval
- Erythropoietin-mimetic peptides
  - long duration of action that allows for once monthly dosing
- Hypoxia-Inducible Factor Stabilizer
  - first oral therapy for the treatment of anemia in CKD