CHRONIC KIDNEY DISEASE (CKD) IN THE UNITED STATES

- Affects one in seven adults, and prevalence is on the rise due to the aging population and obesity.
- Main risk factors: diabetes and hypertension.
- More prevalent in Black, Hispanic and Native American populations.

ANEMIA OF CKD
Progressive worsening anemia as kidney function declines.

<table>
<thead>
<tr>
<th>CKD Stage</th>
<th>eGFR (mL/min/1.73 m²)</th>
<th>Prevalence of Anemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1</td>
<td>≥90</td>
<td>8.4%</td>
</tr>
<tr>
<td>Stage 2</td>
<td>60-89</td>
<td>12.2%</td>
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<tr>
<td>Stage 3a/b</td>
<td>30-59</td>
<td>17.4%</td>
</tr>
<tr>
<td>Stage 4</td>
<td>15-29</td>
<td>50.3%</td>
</tr>
<tr>
<td>Stage 5</td>
<td>&lt;15</td>
<td>53.4%</td>
</tr>
</tbody>
</table>

CLINICAL COMPLICATIONS OF CKD-ANEMIA

- Symptomatic weakness, fatigue and cold intolerance.
- Progressive CKD with higher risk of dialysis.
- Increased cardiovascular risk.
- Increased risk of acute hospitalization.
- Increased risk of all-cause death.

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CONNECTION BETWEEN KIDNEY FUNCTION AND ANEMIA

Kidneys produce erythropoietin (EPO)
- EPO production is stimulated by hypoxia within the interstitial fibroblast cells of the kidney via a negative feedback loop.
- EPO stimulates red blood cell (RBC) production within the bone marrow.
- EPO partially blocks hepcidin, thus allowing increased functional iron availability.

Iron deficiency develops as kidney function worsens.

Late-stage CKD
- Uremia develops, causing inflammation and blunting the effects of erythropoiesis-stimulating agents (ESAs) even further.
- Uremia causes poor nutritional absorption, decreasing intake of dietary iron, folate and vitamin B12.

Anemia
- Occurs when level of RBCs is reduced.
- Anemia develops due to:
  - Acute or chronic bleeding or hemolysis.
  - Lack of EPO stimulation, usually seen in late-stage CKD or with infection/inflammation.
  - Functional iron deficiency.
  - B12 or folate deficiency.

MEASUREMENT OF CKD AND ANEMIA

Evaluating CKD

Kidney dysfunction is:
• Monitored through the glomerular filtration rate (GFR) and categorized by stages 1 to 5.
• Measured indirectly by sampling serum creatinine (Scr) and estimating GFR (eGFR). Commonly done by utilizing the Modification of Diet in Renal Disease (MDRD) equation.

EVALUATING ANEMIA

Laboratory monitoring includes:

Complete blood count (CBC):
• Hematocrit (Hct): volume by percentage (%) of RBCs.
• Hemoglobin (Hgb): protein within the RBC; not affected by volume changes and thus valuable in CKD patients due to frequent volume fluctuations.
• Mean corpuscle volume (MCV): low MCV may be indicative of iron deficiency; high MCV may be indicative of B12/folate deficiency.

B12 and folate levels: water-soluble vitamins essential for the maturation of an RBC; deficiencies can cause a macrocytic anemia. Low levels can be supplemented orally or intravenously.

Iron studies:
• Ferritin: intracellular protein that is the primary form of iron storage in the body, releasing iron to be utilized in a controlled manner; ferritin is an acute phase reactant and is increased in inflammation/infection.
• Iron: measures the amount of iron that is bound to transferrin circulating in the body; unbound ionized iron is toxic to the body, so iron must be bound by transferrin to be moved from storage to the bone marrow for RBC production.
• Total iron binding capacity (TIBC): measures the total amount of transferrin available.
• Iron saturation %: percentage of available iron to be used for RBC production (calculated with formula: [serum iron x 100 / TIBC]).
• Hepcidin: the key regulator of iron metabolism through control of how much iron is transported from storage to be utilized for production of RBCs. Inflammation/infection increases hepcidin levels, which block iron transport, and is greatly responsible for reduced functional iron availability. EPO partially buffers/blocks hepcidin levels, which assists in allowing iron to be used for RBC production. Hepcidin is currently not a blood test that is commonly available.

Retic count: measurement of immature RBCs and used as an indicator that RBCs are being produced by the bone marrow. A low retic count indicates blunting of RBC production. Consequently, a high retic count is indicative of rapid RBC production.

C-reactive protein (CRP): protein produced by the liver which is an acute phase reactant, and thus is increased by inflammation/infection.

EPO: Although not commonly measured for standard anemia work ups, EPO levels can be utilized for hyporesponsive anemia treatments to determine if there is enough EPO being produced by the kidneys or in the evaluation of polycythemia to help determine if there may be excessive production of EPO.

Stool guaiac: basic test to determine if there is blood in the stool that might indicate gastrointestinal bleeding. Low serum iron levels are often indicative of chronic GI bleeding.
NOTES ABOUT ESAs

- Given intravenously (IV) or subcutaneously (SQ).
- Can be expensive and often need prior authorization from insurance.
- Most effective for RBC production if adequate iron, B12 and folate stores.
- Efficacy is blunted by systemic infection/inflammation.
- Takes one to two weeks to see effective RBC increase from any injection in an ideal situation.

ORAL OR INTRAVENOUS IRON?

- Oral iron can take weeks or months to bring up iron stores adequately and can have GI side effects. Often best used if levels are normal/slightly low.
- Intravenous iron can be utilized if iron levels are very low or in the presence of severe anemia. These are usually loaded over multiple days followed by maintenance dosing, with levels being monitored.

TREATING KIDNEY DISEASE

- Determine the cause of kidney disease, including if there is an acute component to it. Clinical situations that can cause acute kidney disease (e.g., infection or inflammation) can also have an impact on and worsen anemia. Find and treat the underlying cause.
- Monitor the stage of the kidney disease, keeping in mind that anemia caused by the kidneys worsens in late-stage CKD (3+).
- The healthier and more stable you can keep a patient’s kidney function, the better off their anemia will be.
- In late-stage CKD, consider starting clinically available erythropoietin-stimulating agents (ESAs), which are commercially produced recombinant EPO.

TREATING ANEMIA

- Measure iron levels, and supplement if low.
- Measure B12/folate levels, and supplement if low.
- ESA dosing given as above.
- If patient has severe/critical anemia or is unstable clinically, then consider blood transfusion and work up for cause.
- Treat aggressively any sign of acute infection/inflammation.
- If stools are guaiac positive, consider referral to GI specialist.
- If hyporesponsive effect to therapy, consider referral to hematology specialist.

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Non-dialysis patients, CKD stage 1-5
- Evaluation and treatment as listed above.
- Monitor for iron deficiency and degree of CKD more often as kidney function declines.
- Have patients followed closely at a CKD/anemia clinic to monitor labs, and obtain ESA and IV iron if needed.

Dialysis patients, CKD stage 6
- Hemodialysis (HD)
  - Iron deficiency and anemia is more pronounced than in non-dialysis patients due to extra loss of blood during dialysis sessions, frequent phlebotomy and increased risk of GI bleeding from uremia and the use of anticoagulation during hemodialysis.
  - Iron and ESA therapies can be given during hemodialysis treatments.
- Peritoneal dialysis (PD)
  - No loss of blood during dialysis, as therapy is non-vascular, and no anticoagulation is used during treatments; however, PD has same frequency of phlebotomy and increased risk of GI bleeding from uremia.
  - ESA therapy is given SQ, and IV iron must be scheduled to be given during PD clinic visits.

NOVEL THERAPIES:
HYPOXIA-INDUCIBLE FACTOR PROLYL HYDROXYLASE INHIBITORS (HIF-PH INHIBITORS)

- Increases EPO production by interfering with the oxygen-sensing pathway of EPO.
- Normally EPO secretion is stimulated during hypoxia and is less active during normoxia. HIF-PH inhibitors block HIF, allowing for expression of target genes to produce EPO even in a non-hypoxic state. This increases the hormonal activity of EPO within the bone marrow to stimulate RBC production.
- Appears to decrease hepcidin concentrations as well, improving the bioavailability of systemic iron for RBC production.