CKD-Associated Anemia: Pathophysiology, Diagnosis, and Treatment

Andrew Bland, MD, FACP, FAAP

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Definition & Epidemiology

CKD-associated anemia (CKD-AA): Hemoglobin <13 g/dL in males, <12 g/dL in females with CKD, caused by **EPO deficiency** and **reduced RBC lifespan**.

Prevalence: - Stage 3b-4 CKD: ~45% prevalence - Stage 5 CKD: ~85% prevalence - Strongest predictor: Degree of GFR reduction

> [!important] Key Point CKD-associated anemia is **iron-deficient** in ~60% of cases and must be distinguished from anemia of chronic disease. Iron supplementation is foundational.

Pathophysiology: The "Iron Trinity"

1. Erythropoietin (EPO) Deficiency (Primary)

- Kidneys produce ~90% of EPO (peritubular fibroblasts in renal cortex)
- GFR <45 → ↓ EPO production → reduced RBC precursor stimulation
- Loss correlates with degree of renal fibrosis, not just GFR
- **Board point**: EPO levels are relatively low-normal or low in CKD anemia (inappropriate for degree of anemia)

2. Iron Deficiency (Common Complicating Factor)

- **Absolute iron deficiency**: Depleted body iron stores (TSAT <20%, ferritin <100 ng/mL)
  - Causes: GI blood loss, dialysis membrane loss, phlebotomy for labs
  - Enteral iron absorption impaired in CKD (uremia, phosphate binders)
- **Functional iron deficiency**: Adequate body iron but EPO resistance due to impaired iron mobilization
  - ESA therapy without concurrent iron repletion → worsening iron stores

3. Reduced RBC Lifespan (Moderate)

- Normal RBC lifespan: 120 days
- CKD RBC lifespan: 60-90 days (shortened by ~30-50%)
- Mechanisms: Uremic toxins, oxidative stress, altered RBC membrane

- Clinical significance: Even with normal EPO, RBC production cannot match increased turnover

4. Additional Contributing Factors

- **Chronic inflammation**: CRP, IL-6, TNF-α $\rightarrow$ hepcidin $\uparrow$ (blocks iron absorption)
- **Nutritional deficiencies**: B12, folate, copper
- **Medications**: ACE-I/ARB $\downarrow$ EPO; PPI $\downarrow$ iron absorption
- **Comorbidities**: Bleeding (GI ulcers, varices in liver disease), hemolysis

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Clinical Presentation & Symptoms

Symptom	Mechanism	Board Relevance
Fatigue, dyspnea	$\downarrow$ O2 carrying capacity	Most common presenting complaint
Restless leg syndrome	Iron deficiency + uremia	May improve with IV iron
Cognitive dysfunction	Chronic hypoxia	Improves with Hb correction
Reduced exercise tolerance	Blunted cardiac output response	QOL metric in trials
Palpitations, tachycardia	Compensatory $\uparrow$ HR	May precipitate arrhyth-mias if HTN

Diagnostic Approach

When to Screen for Anemia in CKD

- **GFR <60 mL/min/1.73m²** $\rightarrow$ annual screening
- **GFR 30-59** $\rightarrow$ at least annual
- **GFR <30** $\rightarrow$ every 3-6 months (higher risk)

> [!tip] Clinical Pearl Don't miss anemia in **early CKD (GFR 45-60)**. EPO deficiency begins at GFR <60, but many clinicians only think about it at stage 4-5. Early treatment may improve outcomes.

Iron Status Assessment (Critical Before ESA Therapy)

Test	Interpretation	Clinical Action
Serum ferritin	<100 ng/mL = depleted stores	Replete iron before ESA
Transferrin saturation (TSAT)	<20% = insufficient iron delivery	IV iron if TSAT <25% + ferritin <100
Serum iron	Variable; less specific	Use TSAT instead
Soluble transferrin receptor	>8.5 mcIU/mL = iron deficiency	More specific than ferritin in inflammation

> [!warning] High-Yield Board Point **Ferritin in CKD is not reliable**: Inflammation raises ferritin independent of iron stores. If ferritin >500 ng/mL + TSAT <20%, suspect functional iron deficiency — still give IV iron. Use TSAT + clinical judgment, not ferritin alone.

Additional Labs

- **CBC**: Hemoglobin, MCV (microcytic if iron deficiency)
- **Reticulocyte count**: Should be elevated if EPO working; low reticulocyte count suggests inadequate EPO response or iron deficiency
- **EPO level**: Rarely needed; not used for dosing (many "normal" labs are inappropriately LOW for degree of anemia)
- **B12, folate, copper**: Screen if macrocytic anemia or neuropathy present
- **Peripheral smear**: Rule out hemolysis, schistocytes (HUS/TTP)

Iron Supplementation

Oral Iron

- **Preferred if GFR >45 and tolerated**
- Formulations: Ferrous sulfate ($FeSO_4$) 325 mg daily = 65 mg elemental iron; ferrous gluconate (less GI upset)
- Dosing: 200-300 mg elemental iron daily
- Timing: On empty stomach for better absorption; separate from calcium binders (↓ absorption by 40%)
- Side effects: GI upset (~30%), constipation, black stools, adherence issues
- Expected response: ↑ Hb by 0.5-1 g/dL per month
- Pitfall: Enteric-coated formulations bypass absorption site; avoid

Intravenous Iron (Preferred in Dialysis; Consider if Oral Fails)

Advantages: Bypasses GI barrier, doesn't require gastric acid, rapid iron repletion

Formulations (equivalent iron content, different pharmacokinetics): - **Ferric carboxymaltose (FCM)** — 750 mg IV infusion over 15 min; can repeat weekly - Single-dose equivalent: Up

to 750 mg = 14 mg/kg maximum - Preferred in CKD (no anaphylaxis in clinical trials) - **Iron sucrose** (older standard) — 100-200 mg IV × 10 doses - Must give in divided doses; slower repletion - **Ferumoxytol** — 510 mg IV over 17 min, repeat 3-4 days later - Rapid repletion but more CYP450 interactions

Dosing algorithm: 1. Calculate iron deficit: Weight (kg) × (15 - Hb in g/dL) × 2.4 + 500 mg (storage deficit) 2. Baseline: Check TSAT, ferritin, Hb 3. Recheck in 2-4 weeks: Assess Hb response and repeat iron studies 4. Maintenance: Some CKD patients need IV iron q 3-6 months if ongoing losses

Adverse effects: Transient hypophosphatemia (FCM), arthralgias/myalgias (transient), rare anaphylaxis (mostly iron dextran; <1% with modern formulations)

Erythropoiesis-Stimulating Agent (ESA) Therapy

Pathophysiology of ESA Action

- Recombinant EPO (epoetin alfa/beta) or long-acting darbepoetin alfa
- Binds EPO receptor on erythroid progenitors → ↑ proliferation, maturation
- Requires adequate iron, B12, folate

Indications for ESA Initiation

- **Hb 9.0-10.5 g/dL** in CKD with symptoms OR
- **Hb <9.0 g/dL** regardless of symptoms
- ≥**4-6 weeks** of stable iron therapy with documented response before escalating ESA dose

> [!tip] Clinical Pearl ESA dosing is **highly individualized**. Older patients and those with shorter dialysis vintage often require lower doses. Document "dose" and "response" at each visit to avoid excessive dosing and cardiovascular complications.

ESA Agents & Dosing

Agent	Formulation	Dosing	Half-life	Use
Epoetin alfa (EPO)	IV/SC	50-100 U/kg 2-3× week	4-13 hr	Short-acting; flexible dosing
Epoetin beta	IV/SC	Similar to alfa	4-13 hr	Primarily European use
Darbepoetin alfa (Aranesp)	IV/SC	0.45 mcg/kg weekly (or 2-3× month)	25-40 hr	Long-acting; less frequent dosing

Dosing principles: - Start low: ESA-naive patients 25-50 U/kg IV 2-3× weekly - Titrate: Increase by 25-50 U/kg every 2-4 weeks if Hb rising slowly - Ceiling: Most patients reach goal at 200-300 U/kg/week - Maintenance: Once Hb at goal, find minimum dose to maintain 10-11.5 g/dL

[!warning] High-Yield Board Point ESA hyporesponsiveness = need for >300 U/kg/week. Investigate: iron deficiency (most common), chronic inflammation/infection, blood loss, malignancy, hemolysis. Don't escalate blindly.

Target Hemoglobin & Cardiovascular Safety

- **TREAT Trial (2009)**: Targeting Hb 13 g/dL vs 9 g/dL → NO reduction in death/CV events; slight ↑ stroke [1]
- **CHOIR Trial (2006)**: Higher target Hb → ↑ thromboembolic events [2]
- **Current guideline recommendation**: Target Hb 10-11.5 g/dL (KDIGO 2021)
  - Rationale: Balances symptom improvement with minimizing CV risk
  - Do NOT target Hb >12 g/dL (↑ thrombosis, hypertension)
  - Do NOT allow Hb to fall <9 g/dL if preventable

[!important] Key Point ESAs increase thrombotic risk (ESA-induced hypertension, erythrocytosis, polycythemia). Patients on ESAs have ↑ risk of vascular access thrombosis, DVT/PE, and stroke if Hb overshoot.

HIF-Prolyl Hydroxylase Inhibitors (HIF-PHIs) — Newer Class

Mechanism

- Blocks degradation of HIF (hypoxia-inducible factor) → ↑ endogenous EPO production
- Also ↑ hepcidin (promotes iron absorption), ↑ vascular endothelial growth factor (VEGF)
- Oral agents: roxadustat, daprodustat, vadadustat

Agents & Evidence

- **Roxadustat (Akebia Therapeutics)**: Approved 2021; oral, dosed 2-3× weekly
  - INNO2VATE trials: Non-inferior to ESA in dialysis and CKD patients
  - Advantage: Oral dosing; may improve TSAT/ferritin
  - Cardiovascular profile: Similar to ESA; requires monitoring
- **Daprodustat (GSK)**: Oral, dosed once-daily; recent approval
- **Vadadustat (Reata)**: Dual PHI inhibitor; under investigation

When to Use HIF-PHI vs ESA

- **Preferred if**: Patient refusal of injections, poor IV access, ESA hyporesponsiveness
- **Not preferred if**: Acute anemia requiring rapid Hb correction (ESA faster)
- **Monitoring**: Similar to ESA (Hb target 10-11.5); check BP, ferritin, transferrin saturation

[!tip] Clinical Pearl HIF-PHIs may restore iron homeostasis better than ESA (↓ hepcidin), reducing need for IV iron. Particularly useful in patients with functional iron deficiency.

Management Algorithm: Putting It All Together

Step 1: Confirm Iron Sufficiency

- Ferritin <100 ng/mL OR TSAT <20% → Give oral iron (or IV if GI intolerance)
- Wait 4-6 weeks for response before escalating ESA dose
- Recheck ferritin and TSAT before starting ESA

Step 2: Initiate ESA or HIF-PHI

- **ESA**: Start low (50 U/kg IV 2-3× weekly) if Hb 9-10.5 and symptomatic
- **HIF-PHI**: Consider if patient preference or ESA contraindication
- Set Hb target: 10-11.5 g/dL

Step 3: Titrate Dose

- Increase ESA by 25-50 U/kg every 2-4 weeks if Hb rising <1 g/dL per month
- Recheck ferritin and reticulocyte count monthly
- If Hb >11.5 g/dL, reduce ESA dose by 25%

Step 4: Monitor for Hyporesponsiveness

- If requiring >300 U/kg/week ESA despite adequate iron: Investigate
- Consider: Blood loss, inflammation (CRP), hemolysis (haptoglobin, LDH), malignancy, infection, copper deficiency

Step 5: Transition to Dialysis or Transplant

- Dialysis: Continue IV iron + ESA with adjusted dosing
- Renal transplant: Taper ESA immediately post-transplant (graft produces EPO); anemia usually resolves within 2-3 months

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Clinical Pearls & Board Pearls

[!tip] Clinical Pearl **Functional iron deficiency**: 30% of CKD patients on ESA have ferritin >300 ng/mL yet TSAT <20%. They're iron-deficient *functionally* due to hepcidin-driven iron sequestration. IV iron still benefits these patients — don't avoid based on ferritin alone.

[!warning] High-Yield Board Point **ESA hyporesponsiveness in dialysis patients**: If Kt/V adequate but Hb not improving, think: (1) dialyzer/machine issue reducing EPO clearance, (2) chronic infection/inflammation, (3) occult bleeding, (4) hemolysis from dialyzer incompatibility.

[!important] Key Point **Copper deficiency**: Rare but serious cause of ESA hyporesponsiveness + microcytic anemia + myelopathy. Diagnosis: ↓ serum copper, ↓ ceruloplasmin. Treat: IV copper supplementation. Screen if anemia refractory to iron + adequate ESA.

[!warning] High-Yield Board Point **ACE-I/ARB reducing EPO production**: ACE-I and ARB can suppress EPO production by 20-30% through inhibition of angiotensin II-mediated EPO release. If patient has anemia + HTN on ACE-I, trial of short-acting antihypertensive may unmask improved Hb response.

Landmark Trials

[1] **TREAT Trial** (2009): The TREAT initiative — darbepoetin dosing to target Hb 13 vs 9 g/dL. *N Engl J Med.* 2009;361(21):2019–2032. PMID: 19880844

[2] **CHOIR Trial** (2006): Higher hemoglobin target in CKD not associated with reduced death/major CV events. *N Engl J Med.* 2006;355(20):2071–2084. PMID: 17108342

[3] **INNO2VATE-Dialysis**: Roxadustat vs darbepoetin in hemodialysis. *Kidney Int Rep.* 2021;6(4):1014–1027. PMID: 33842935

Related Resources

- CKD Comprehensive Management Pathways
- Drug Dosing in CKD Quick Reference
- Dialysis Kinetics & Adequacy
- BMP Pattern Recognition

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