

Anemia of CKD

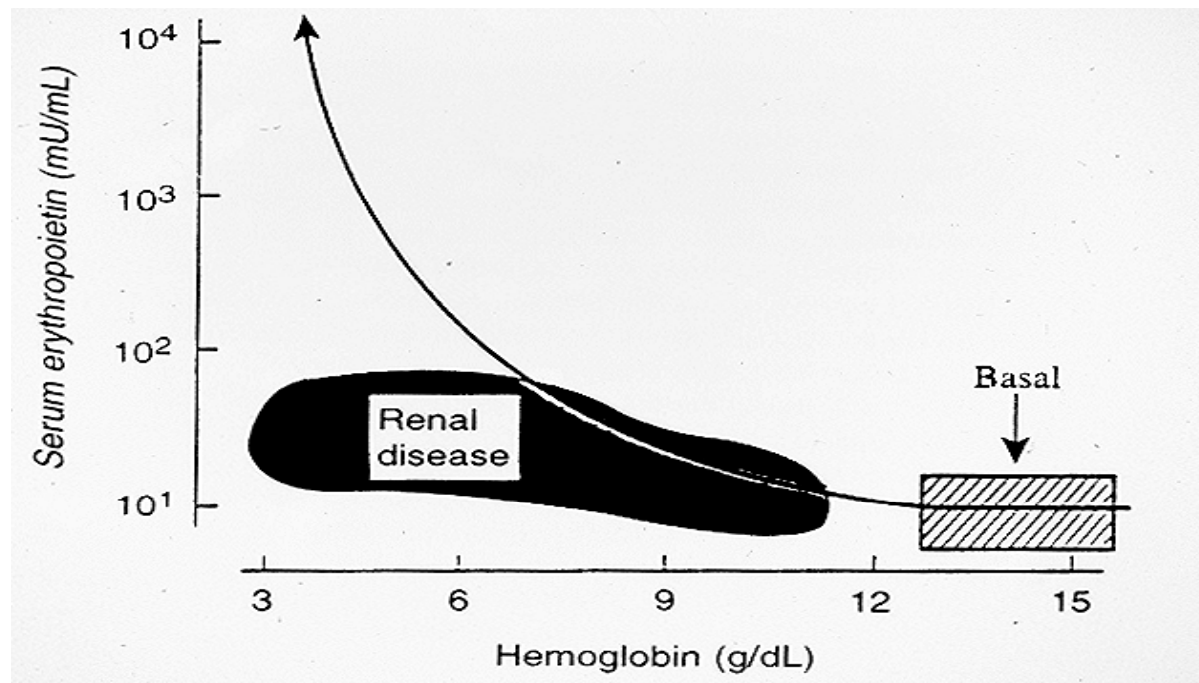
Andrew E. Briglia, D.O.
Annapolis Nephrology Associates.

Epidemiology

- NHANES: Anemia defined as Hb <11 g/dL.
- Prevalence per stage CKD:
 - III 1.3%
 - IV 5.2%
 - V 44.1%

Astor BC et al. Arch Int Med 2002;162(12):1401-1408.

Erythropoietin Levels in Anemia

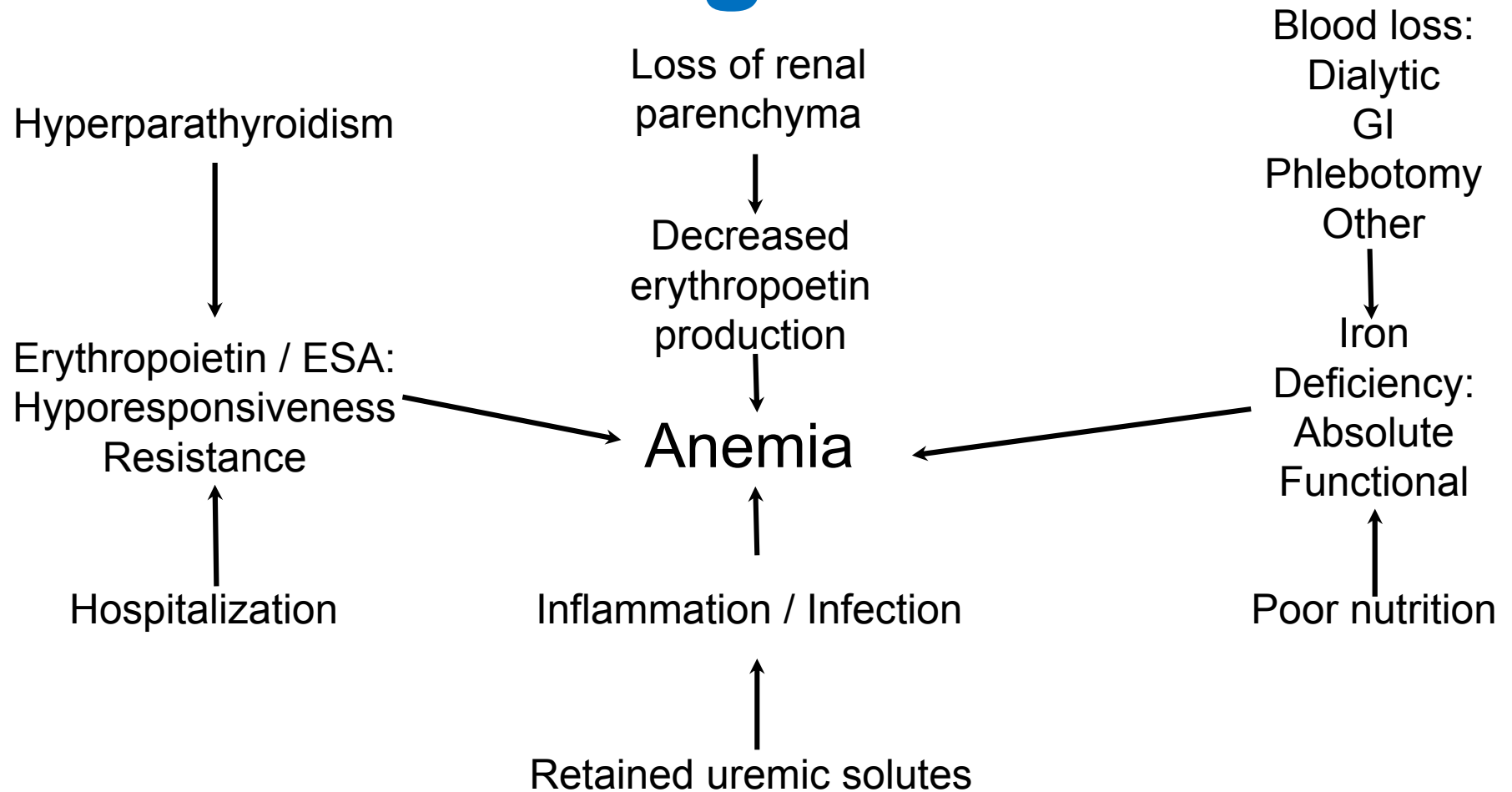


Hillman 'Hematology in Clin Prac,' Mcgraw-Hill, 1995

Erythropoietin

- Glycoprotein hormone: 165 amino acid peptide, 4 carbohydrate chains
- Produced by renal peritubular interstitial cells.
- Reduces apoptosis of erythroid precursors.
- Circulating levels induced by anemia or tissue hypoxia. Levels variable in CKD.

Anemia of CKD: Pathogenesis



Diagnosis of Iron Deficiency

1. Bone marrow studies.
2. Serum iron
 - interlaboratory variability.
 - diurnal variation.
 - rapid decrease most often seen in acute inflammation.
 - not a useful diagnostic test by itself.
3. Serum Ferritin (Apo ferritin, Hemosiderin)
 - storage protein complex in RE cells (liver, spleen, bone marrow).
 - correlates fairly well with whole-body iron storage.

Diagnosis of Iron Deficiency

Serum Ferritin

- Does not allow for accurate estimation of functional iron requirements in ESA- treated patients.
- Potent acute phase reactant (infection, malignancy, connective tissue ds, liver ds, smoking, ETOH).
- Occult inflammation in ESRD.
- Mittal et al: <100 ng/mL (48% sens., 75% spec).
- Kalantar-Zadeh et al: 200 ng/mL (41% sens, 100% spec).

Diagnosis of Iron Deficiency

4. Transferrin Saturation (TSAT)

- Represents protein-bound iron in circulation.
- $[P_{\text{Fe}} / \text{TIBC}] \times 100\%$
- TIBC affected by transferrin.
- Transferrin altered by factors other than iron status (malnutrition, negative acute-phase reactant).
- Kalantar-Zadeh et al: <20% (88% sens., 63% spec.)
- Mittal et al: 21% (81% sens., 63% spec.)

Diagnosis of Iron Deficiency

5. Serum Soluble Transferrin Receptor Assay (sTfR)
 - Truncated form of receptor released into circulation in response to iron deficiency.
 - Inconsistent results in clinical trials.
6. Percent Hypochromic RBCs (PHRC)
 - > 10% predicts response to IV iron.
 - Good predictor of ability to ↓ ESA after iron.
 - Reflection of Hgb concentration rather than content.
7. Reticulocyte Hemoglobin Content (CHr)
 - CHr < 26 pg accurate predictor of iron deficiency in HD patients (80% sens., 80% spec.).

Absolute Iron Deficiency

Reduction in bone marrow RE iron.

Defined by low TSAT (<20%) and Ferritin (<100 ng/mL).

Develops rapidly in patients treated with ESA.

1998 ESRD Core Indicators Project:

30% patients TSAT < 20%.

19% patients Ferritin < 100 ng/mL.

Functional Iron Deficiency

Consequence of ESA therapy.

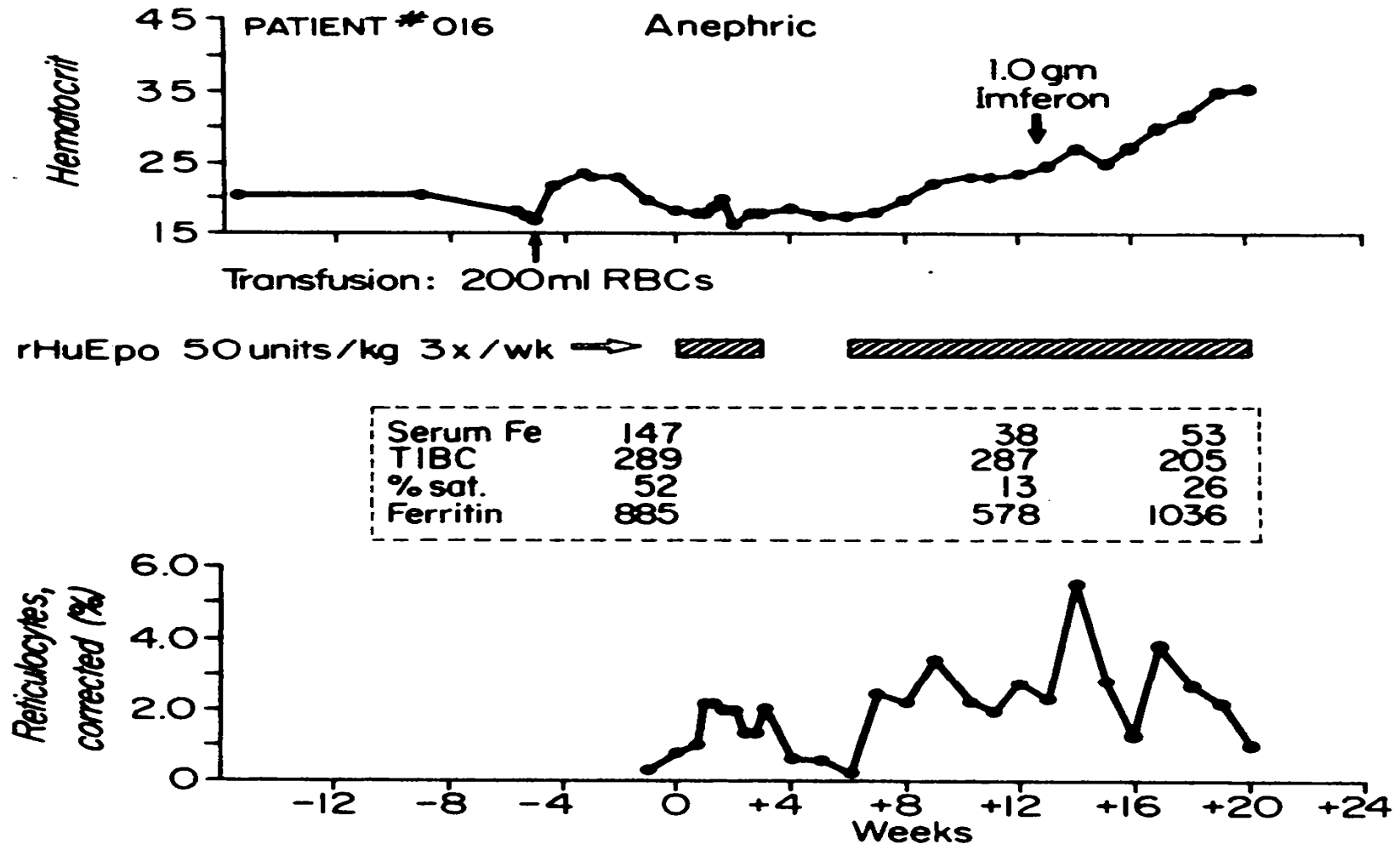
Iron uptake by erythroid precursors exceeds capacity of RE system to release iron to transferrin (“reticuloendothelial block”)

TSAT falls much faster than ferritin

RBCs produced with ↓Hgb content and ↑protoporphyrin

Corrected with IV iron.

Functional Iron Deficiency



Eschbach, JW. Seminars in Dialysis. 12(4), 212.

Oral Iron Preparations

Preparation	Elemental Iron (mg)	Comment
Ferrous sulfate	65	
Ferrous gluconate	38	
Chromagen soft gel	66	fumarate; 250 mg vit C
Feosol Caps	50	sulfate; time release
Feosol Tabs	65	sulfate; time release
Fergon Plus Caps	58	gluconate; 75 mg
Nu-Iron 150 Caps	150	polysaccharide
Niferex-150 Forte	150	polysaccharide
Slow-Fe Tabs	50	sulfate; time release
Tabron	100	fumarate
Proferrin	11	heme iron polypeptide

Nissenson AR, Spivale JL: Erythropoiesis, Iron, and Epoetin alfa Therapy, 1997, p.16.

IV Iron Repletion

- Goal: 1 gram elemental iron over 3-4 infusions, each spaced 1-2 weeks apart
- Use when transferrin saturation <20% or when serum ferritin <100 ng/mL (200 ng/mL in dialysis patients).
- Iron dextran (Dexferrum, Imferon, INFeD)
- Iron sucrose (Venofer: 100 mg/5 mL)
- Sodium ferric gluconate complex (Ferrlecit: 62.5 mg/5 mL)
- Ferumoxytol (Feraheme: 510 mg)

ESA Administration

- Generally reserved for Hb <10g/dL
- Epoetin alfa (Epogen, Procrit): 50-100 U/kg IV (thrice weekly) or 75-100 U/kg SC (weekly)
- Darbepoetin alfa (Aranesp): 0.45 mcg/kg IV/SC weekly or 0.75 mcg/kg SC every other week.
- Epoetin beta: Continuous Erythropoiesis Receptor Activator (CERA)
- ESA hyporesponsive: 150-300 U/kg IV thrice weekly (or equivalent).
- ESA resistant: Failing to reach target Hb with higher dose.

Causes for ESA

Hyporesponsiveness / Resistance

1. Iron deficiency: Most common
2. Infection/inflammation (vascular access, surgical inflammation, AIDS, SLE, MI, DM)
3. Chronic blood loss (hemodialysis, GI loss, hemolysis)
4. Hyperparathyroidism (osteitis fibrosa)
5. Aluminum toxicity
6. Hemoglobinopathies (alpha and beta thalassemias, sickle cell anemia)
7. Malnutrition (folate or vitamin B12 deficiency)
8. Multiple myeloma
9. Inadequate dialysis (uremic toxins)
10. Medications (myelosuppressive agents, ACE-i/ARB)

Comparison of Trials

<p>¹CHOIR: CKD 3-4</p>	<p>N = 1432 A. Hb 13.5 (n=715) B. Hb 11.5 (n=717)</p>	<p>Primary endpoint: Composite of death, MI, CHF hospitalization, and CVA: A: 125 B: 97 Similar QOL in both groups</p>
<p>²CREATE: CKD 3-4</p>	<p>N = 603</p>	<p>Nonsignificant trend toward higher incidence of CV events and shorter dialysis-free survival with full (Hb 13-15) vs. partial (Hb 10.5-11.5) anemia correction</p>
<p>³TREAT: CKD/DM(2)</p>	<p>N = 4038 Darbepoetin: 2012 Placebo: 2026</p>	<p>No significant difference in composite endpoint (death, CV event, ESRD). Target Hb 13 Excess of CVA in darbepoetin group (101 vs. 53, p<0.001)</p>

¹Singh AK, Szczech L, Tang KL, et al; N Engl J Med. 2006;355(20):2085-2098.

²Drueke TB, Locatelli F, Clyne N, et al; N Engl J Med. 2006;355(20):2071-2084.

³Pfeffer MA, Burdmann EA, Chen CY, et al; N Engl J Med. 2009;361(21):2019-2032.

Conclusions

- Quality of life and metrics for physical domains may improve when CKD patients are treated with ESA.
- Treatment of anemia of CKD with ESA has been inconsistently associated with improved surrogate outcomes (possible reduction in LV mass and improved CV morbidity).
- Recent data suggest that full (vs. partial) treatment of anemia does not provide survival benefit, and may in fact impose harm.