ASN DIALYSIS ADVISORY GROUP

ASN DIALYSIS CURRICULUM

Anemia, Iron, and Erythropoietin

Jeffrey S. Berns, MD, FASN
Perelman School of Medicine
University of Pennsylvania

Outline

- Prevalence of anemia of CKD
- Pathophysiology of anemia of CKD
- Treatment
  - Iron
  - Erythropoiesis stimulating agents
- Goals and Benefits of Treatment
- Risks of Treatment

Prevalence of Anemia in Patients with CKD

- Anemia (Hgb < 13.0 g/dl in men, < 12.0 g/dl in women)
- Typically begins to develops with eGFR < 60 ml/min/1.73m^2
- Prevalence increases at lower eGFR levels
  - Hgb < 13 g/dl in ~ 20% of patients with CKD and eGFR 45-60 ml/min/1.73m^2
  - Hgb < 13 g/dl in ~ 90% of patients with CKD and eGFR 15 ml/min/1.73m^2
- At any level of GFR, anemia tends to be more severe in women, African-Americans, and diabetics

Evaluation of Anemia in Patients with CKD

- Recommended testing includes:
  - Complete blood count
  - Red blood cell indices
  - White blood cell count and differential
  - Absolute reticulocyte
  - Vitamin B12 and folate levels
  - Serum ferritin, transferrin saturation (TSAT)

  - Other tests as indicated, particularly if anemia seem “out of proportion” to severity of CKD, assess for other causes, i.e. Hgb < 9-10 g/dl with eGFR > 30 ml/min/1.73m^2

- Serum erythropoietin level testing is not recommended
- Evaluate as clinically indicated if iron deficiency is present

Pathophysiology of Anemia in CKD

- Impaired synthesis of erythropoietin (EPO) from renal cortical peritubular interstitial fibroblast-like cells
- EPO is a 165 amino acid glycoprotein
- CKD Leads to relative EPO deficiency
  - Blood levels often in “normal” range but do not increase to levels seen in most other anemias
- Renal EPO synthesis is stimulated by hypoxemia/anemia
  - Hypoxemia stabilizes hypoxemia-inducible factor (HIF) complex that is degraded at higher oxygen levels
  - HIF complex is an EPO gene transcription factor

Pathophysiology of Anemia in CKD

- In presence of anemia/hypoxemia, HIF increases transcription of EPO gene

- EPO stimulates erythropoiesis in bone marrow
  - Binds to EPO receptor on erythrocyte progenitor cells in bone marrow
  - Activates signaling cascade increases reduces apoptosis of CFU-E and other progenitor cells that develop into mature erythrocytes
  - Also appears to increase life span of young red blood cells/reticulocytes in the circulation

- Iron deficiency is also a common contributing factor
- Inflammation is also a common contributing factor, especially in hemodialysis patients

- Other causes of anemia—folate and vitamin B12 deficiency, and others are relatively uncommon

Iron Deficiency in CKD Anemia

- Iron is needed to for adequate erythropoiesis and hemoglobin synthesis
- 20-50% of patients with CKD/ESRD may have some degree of iron deficiency
- Iron deficiency can be “true” iron deficiency with inadequate total body and bone marrow iron or “functional” iron deficiency with adequate or increased body/bone marrow stores that are sequestered in reticuloendothelial cells and not available for erythropoiesis
  - Functional iron deficiency usually associated with infection and/or inflammation
  - Mediated by various inflammatory cytokines and abnormality in iron regulatory protein hepcidin
- Traditional iron tests—serum ferritin and transferrin saturation with iron (TSAT)—are not particularly reliable markers of bone marrow iron stores or responsiveness to IV iron infusion

Iron Deficiency in CKD Anemia

- Hemodialysis patients are particularly likely to have true iron deficiency due to dialysis-related blood loss, blood tests, vascular access surgery, GI tract blood losses

- Hemodialysis patients are also more likely to have infection/inflammation and functional iron deficiency—especially with tunneled dialysis catheter

- Traditional iron tests—serum ferritin and transferrin saturation with iron (TSAT)—are not particularly reliable markers of bone marrow iron stores or responsiveness to IV iron infusion
  - True iron deficiency usually associated with TSAT < 20% and serum ferritin < 100-200 ng/ml
  - With functional iron deficiency, TSAT typically 15-25% and serum ferritin > 300-500 ng/ml

Erythropoiesis Stimulating Agents (ESAs)

- Recombinant human erythropoietin (rHuEPO, epoetin alfa)
  - EPO gene cloned 1985; initial clinical trials with epoetin alfa reported in 1986-1989. Approved by US FDA in 1989.
  - Human gene expressed in Chinese Hamster Ovary system
    - Same amino acid structure and biological activity as native EPO
    - Contains 3 N-linked carbohydrate chains required for biological activity
    - In US, marketed as Epogen® and Procrit®

- Darbepoetin alfa
  - Super-sialylated analog of rHuEPO
  - 5 N-linked carbohydrate chains
  - 5 amino acid substitutions to EPO peptide backbone distant from receptor-binding domain
  - Binds to EPO-receptor with same mechanism of action
  - In US, marketed as Aranesp®

Clinical Use of ESAs

- Dose-dependent increase in Hgb concentration
  - With 50 U/kg epoetin twice/wk and 0.45 mcg/kg darbepoetin once/wk mean time to stable target Hgb concentration is about 7-8 weeks

- Epoetin has shorter pharmacologic and biologic half-life compared to darbepoetin
  - Pharmacologic half-life ~ 8.5 hrs vs. 25 hrs
  - Epoetin alfa ~30% more effective on average by subcutaneous injection vs. intravenous injection
  - Darbepoetin efficacy equivalent with either injection route

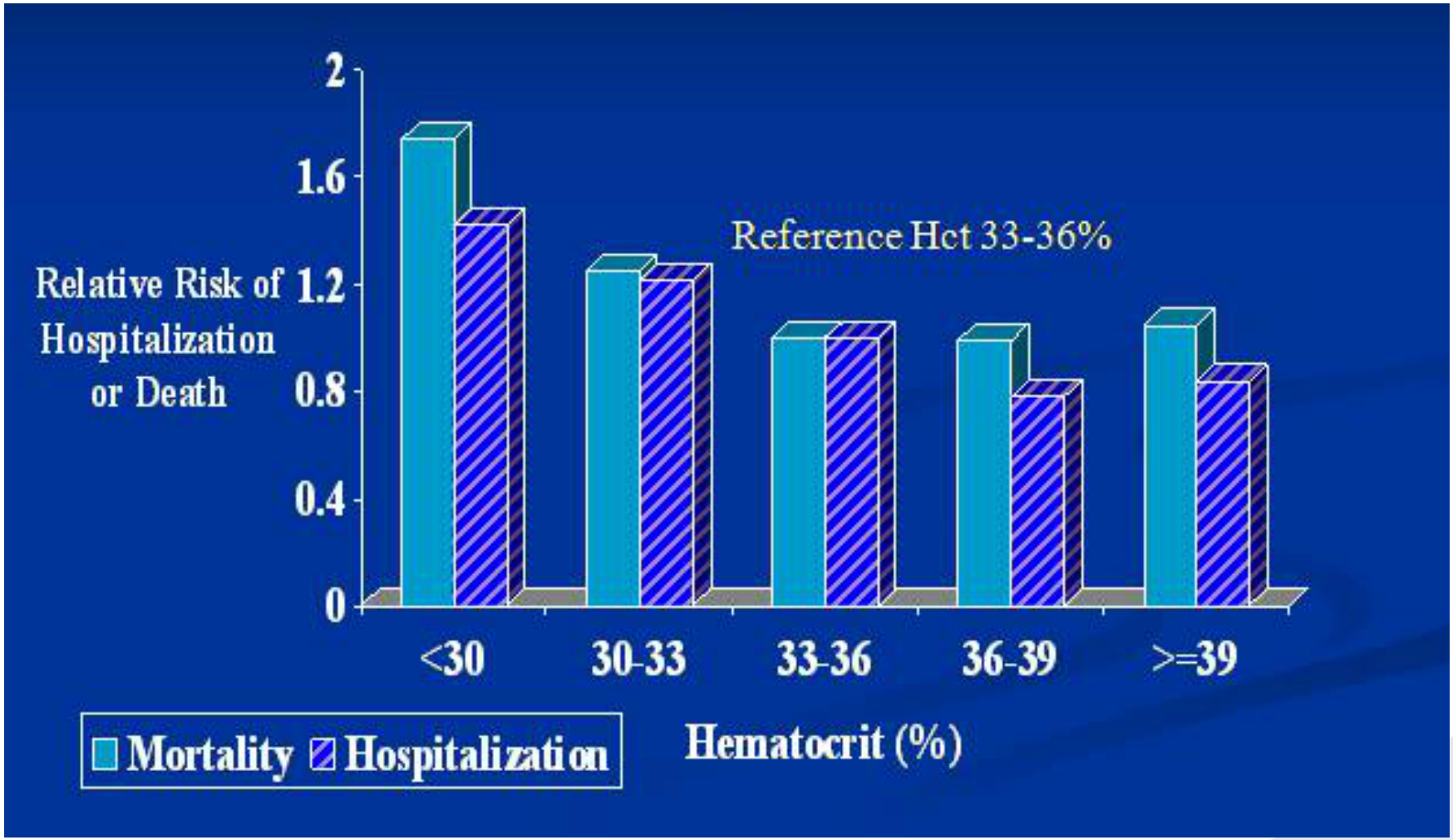
  - Epoetin alfa dosing usually 1-3 times per week
    - 3 times weekly dosing typically for in-center HD patients
  - Darbepoeitin dosing usually once every 1-2 weeks, may be less often

Hemoglobin Target

- When epoetin was first approved for use in patients with ESRD, typical Hgb concentration in chronic HD patients was ~ 5-7 g/dl
  - Average transfusion rate ~ 0.5 units packed red blood cells per patient per month
  - Transfusion-related iron overload was common
  - Injectable androgens also used to stimulate erythropoiesis
- ESAs markedly reduced transfusion needs
- Initial studies demonstrated clinical improvement with increase in Hgb levels to 9-10 g/dl range
- Subsequent retrospective observational cohort studies, mostly in hemodialysis patients, indicated lower hospitalization risk, reduced left ventricular hypertrophy, improved quality of life, and lower mortality associated with even higher Hgb concentrations

Hematocrit and death and hospitalization risk

Collins, et al., JASN 2001



Hemoglobin Target

- Several prospective randomized controlled trials (RCTs) comparing ESA-treated hemodialysis and CKD patients with higher vs. lower Hgb targets and one RCT comparing darbepoetin vs. placebo (with darbepoetin "rescue") in CKD patients did not find benefit of Hgb levels of ~ 12-13 g/dl compared to Hgb levels of 9-11 g/dl

- Quality of life benefits were variable and if present, tended to be of questionable clinical significance

- Transfusion rates reduced 18-40% (but not eliminated)

- Risks associated with higher Hgb levels and/or higher ESA doses needed to achieve the higher Hgb levels
  - Hypertension
  - HD access clotting and other thromboembolic disease
  - Stroke
  - Cancer-associated mortality

The “Normal Hematocrit Study”

Besarab, et al., NEJM 1998

- Randomized, prospective clinical trial in 1233 hemodialysis patients with heart failure or ischemic heart disease (1993-1996)
  - Used epoetin alfa in both groups to target normal or low Hct
    - Normal Hct group—target 42%; Low Hct group—target 30%

- Primary end-point: time to death or first non-fatal MI

- Terminated early by data safety and monitoring committee
  - Difference in event-free survival did not reach prespecified statistical stopping boundary but indicated greater risk in normal Hct group with higher incidence of HD access thrombosis
  - In subsequent final analysis statistically higher risk for death (RR 1.09; 95% CI 1.01-1.40) and composite outcome (RR 1.19; 95% CI 1.03-1.39)

  - Paradoxically, higher mean Hct associated with better survival in both groups

CHOIR

- Open label RCT, 130 U.S. centers, epoetin alfa SC weekly
- CKD (eGFR 15-50 mL/min/1.73m^2); Hgb<11.0g/dL
- High Hgb target: 13.0-13.5 initially; changed → 13.5 g/dL
- Low Hgb target: 10.5-11.0 initially; changed → 11.3 g/dL
- Study terminated early because conditional power for demonstrating a benefit of high Hgb was <5%
- 34% increased risk of composite outcome of death, MI, hospitalization for CHF, stroke
- Similar QoL measures

Singh, et al., NEJM 2006.

CREATE

- Open label, RCT, 94 centers in 22 countries, epoetin beta SC weekly
- CKD (eGFR 15-35 mL/min/1.73m^2); Hgb 11.0-12.5 g/dL

- High Hgb target: 13.0-15.0 g/dL immediately
- Low Hgb target: 10.5-11.5 g/dL after Hgb<10.5 g/dL

- Primary endpoint time to first CV event: sudden death, MI, acute HF, stroke, TIA, angina, PVD with amputation or necrosis, arrhythmia

- No significant difference in risk of composite CV primary end point (HR 0.78; p=0.20) or secondary endpoints, including effects on LVH
- Most QoL measures better in higher Hgb group
  - General health, mental health, physical function, social function, vitality

Drueke, et al., NEJM 2006.

TREAT: Study Design

- Randomized, double-blind, placebo-controlled multicenter study

- Type 2 DM, CKD (eGFR 20-60 mL/min/1.73m^2), Hgb< 11 g/dL, TSAT e15%
  - Patients with CV, major surgery, received an ESA in prior 12 weeks were ineligible
  - Mean age ~67 years; 2/3 with CVD; 20% with MI, 10% with stroke

- 1:1 randomization
  - Algorithm to maintain Hgb ~ 13g/dL in darbepoetin group
  - Placebo group received darbepoetin alfa as a rescue agent if Hgb < 9.0 g/dL; placebo when Hgb e 9 g/dL

TREAT: Results

- Primary cardiovascular composite end point (all-cause death, MI, stroke, heart failure, myocardial ischemia): No difference
  - Of the individual end points only stroke more common in darbepoetin group (Hazard Ratio 1.92, $p < 0.001$)
- Primary renal composite end point (ESRD or death): No difference
- Cardiovascular mortality: No difference

- QOL improvement in darbepoetin group > placebo but mostly minor impact

- More venous and arterial thrombotic events

- More deaths due to cancer in patients with known malignancy

- In subsequent report, initial response predicts risk of cardiovascular events and mortality
  - Poor responders with poorest outcomes; placebo and good responders with similar outcomes

Pfeffer MA, et al. NEJM, 2009.

RCT of ESA Treatment in CKD and ESRD: Conclusions

- In middle-aged patients with CKD and DM and/ or extensive CVD burden, targeting Hgb levels ~ 13 g/dL with ESA appears to cause harm

- In middle-aged patients with CKD and DM and/ or extensive CVD burden, using an ESA to keep Hgb >9-10 g/dL is no worse than higher Hgb levels
  - Any QoL benefit of higher Hgb appears to be inconsistent and of uncertain clinical benefit

- Early response to ESA predicts outcome

- Risks: hypertension, AV access and other thrombotic events, stroke, cancer-associated mortality

- FDA now requires enrollment in a Risk Evaluation and Mitigation Strategy (REMS) Program when treating cancer patients with ESAs

Current US FDA ESA Prescribing Information and "Block Box Warning"

WARNING: ESAs INCREASE THE RISK OF DEATH, MYOCARDIAL INFARCTION, STROKE, VENOUS THROMBOEMBOLISM, THROMBOSIS OF VASCULAR ACCESS AND TUMOR PROGRESSION OR RECURRENCE

Chronic Kidney Disease:

- In controlled trials, patients experienced greater risks for death, serious adverse cardiovascular reactions, and stroke when administered erythropoiesis-stimulating agents (ESAs) to target a hemoglobin level of greater than 11 g/dL.
- No trial has identified a hemoglobin target level, ESA dose, or dosing strategy that does not increase these risks.
- Use the lowest ESA dose sufficient to reduce the need for red blood cell (RBC) transfusions.

Anemia Adjuvant Therapy

- Several agents have been investigated for a role in increasing efficacy of ESA's, allowing reduced doses:
  - L-carnitine
  - Ascorbic acid
  - Vitamin E
  - Androgens
  - Pentoxyfilline
- Their effects on Hgb concentration inconsistent and none have been shown to improve clinical outcomes
- Their use as ESA adjuvants is not recommended

ESA “Resistance” or Hyporesponsiveness

- ESA resistance is rare; but relative hyporesponsiveness—which has been variably define—is common and associated with poorer patient outcomes
  - KDIGO defines initial ESA hyporesponsiveness as failure to increase in Hgb concentration from baseline with one month of ESA treatment using appropriate weight-based dosing. (Not Graded)
  - KDIGO defines subsequent ESA hyporesponsiveness the failure to maintain previously stable Hgb concentration (with stable ESA dose) despite 2 ESA dose increases with a 50% increase in dose from the prior stable dose
- Look for a cause: iron deficiency, infection, inflammation, HD catheter, malnutrition.
  - Take off the socks
- Avoid repeated escalations in ESA dose beyond double the initial (weight-based or otherwise “reasonable”) dose or the dose at which the Hgb had been stable
- As appropriate, trial of IV iron, maintain some ESA, transfuse

Available IV iron preparations (U.S.)

- Most studies have found little or no response to oral iron in hemodialysis and peritoneal dialysis patients. Some patients with CKD not on dialysis may respond to oral iron but response to IV is generally better
  - Ferric citrate is a new iron-containing phosphate binder that also appears to be more effective than other oral iron compounds as an iron supplement—use increases serum ferritin and TSAT with reduced use of IV iron and ESA

- Iron dextran (InFed®, Dexferrum®)
  - Test dose recommended for first administration
- Sodium ferric gluconate complex (Ferrlecit®)
- Iron sucrose (Venofer®)
- Ferrumoxytol (Feraheme®)
- Ferric carboxymaltose (Injectafer®)

} Approved for use with > 500 mg/dose

- All with similar clinical efficacy
- Specific dose prescribing details vary….consult specific iron prescribing information

IV Iron Toxicities

- **Immediate severe "anaphylactoid" reactions**
  - Primarily with iron dextran
  - Not IgE mediated
  - May be direct release of mediators from mast cells
- **Other acute reactions—occur with all IV irons, some dose and rate of infusion related**

  Arthralgias-myalgias

  Anaphylactoid reactions

  Hypotension

  Nausea, emesis

  Urticaria

  Bronchospasm

  Chest, back, abdominal pain

  Death

Chronic IV Iron Toxicities

- **Infection**
  - Some retrospective observational studies have shown ~ 15-35% higher risk of infection-associated death in patients receiving IV iron
  - No prospective studies have demonstrated increased (or decreased) risk of infection or poorer outcomes with infection
  - It is recommended to avoid administering IV iron to patients with active systemic infection

- **Mortality**
  - Older studies suggest no risk of moderate IV iron doses; higher doses may be associated with increased mortality risk
  - No recent prospective studies

- In a recent retrospective study HD patients receiving bolus IV iron (large dose over a short time period) were at increased risk of infection-related hospitalization and mortality compared with patients receiving maintenance IV iron (low doses on a regular basis)
  - Particularly in patients with HD catheter or recent infection
  - Compared with no iron, maintenance dosing was not associated with increased risk

Brookhart, et al. JASN 2013

KDIGO Clinical Practice Guidelines (2012): Treatment with Iron

For adult CKD patients with anemia not on iron or ESA therapy or on who are on ESA therapy and not receiving iron supplementation we suggest a trial of IV iron (or in CKD ND patients alternatively a 1-3 month trial of oral iron therapy) if:

- an increase in Hb concentration without starting ESA treatment is desired and
- TSAT is d30% and ferritin is d500 ng/ml

Guide subsequent iron administration in CKD patients based on Hgb responses to recent iron therapy, as well as ongoing blood losses, iron status tests (TSAT and ferritin), Hgb concentration, ESA responsiveness, and ESA dose in ESA treated patients, trends in each parameter, and the patient's clinical status.

KDIGO Clinical Practice Guidelines (2012): ESA Initiation

For adult CKD ND patients with Hgb concentration e10.0 g/dL we suggest that ESA therapy not be initiated

For adult CKD 5D patients, we suggest that ESA therapy be used to avoid having the Hgb concentration fall below 9.0 g/dl by starting ESA therapy when the Hgb is between 9.0-10.0 g/dl.

For adult CKD ND patients with Hgb concentration <10.0 g/dl we suggest that the decision whether to initiate ESA therapy be individualized

KDIGO Clinical Practice Guidelines (2012): ESA Maintenance Therapy

In general, we suggest that ESAs not be used to maintain Hgb concentration above 11.5 g/dl in adult patients with CKD.

Individualization of therapy will be necessary as some patients may have improvements in quality of life at Hgb concentration above 11.5 g/dl and will be prepared to accept the risks.

In all adult patients with CKD, we recommend that ESAs not be used to intentionally increase the Hgb concentration above 13 g/dl.

Summary and Conclusions

- Anemia is common and potentially severe complication of advanced CKD and ESRD
- The primary etiology of CKD-related anemia is deficiency of the hormone erythropoietin
- Administration of iron and erythropoiesis stimulating agents (epoetin, darbepoetin) can substantially improve anemia in patients with CKD and ESRD
- Recent studies indicated that in most patients target Hgb levels of 10-11 g/dl are appropriate
  - Targeting to higher levels of no benefit and associated with increased risks
- Optimal anemia management requires thoughtful use of both iron (usually IV) and an ESA, with transfusions as indicated
- Important to individualize anemia management in CKD and ESRD patients