Pharmacist’s Guide to Managing Anemia in Chronic Kidney Disease

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Disclosures

• Speaker for Amgen, American Regent

Learning Objectives

• Explain the impact of anemia on quality of life and mortality risk
• Compare and contrast therapies used in the management of anemia in patients with Chronic Kidney Disease (CKD)
• Discuss laboratory tests and monitoring parameters used to evaluate anemia
• Identify a treatment plan for the management of anemia based on patient specific parameters

Anemia: Prevalence

• Anemia affects 30% of the world population
• 3.4 million Americans diagnosed
  – Millions more undiagnosed
  – Most common blood disorder in the US
• Hospitalized patients
  – Within 3 days of admission, > 90% of ICU patients anemic
• Hemodialysis patients
  – 97% anemic


Chronic Kidney Disease

• Any condition that causes reduced kidney function over a period of time. Chronic kidney disease may develop over many years and lead to end-stage renal disease (ESRD).
• The five stages of CKD are:
  – Stage 1: Kidney damage with normal kidney function (estimated GFR ≥90 mL/min) and persistent proteinuria (≥3 months.)
  – Stage 2: Kidney damage with mild loss of kidney function (estimated GFR 60-89 mL/min) and persistent proteinuria (≥3 months).
  – Stage 3: Mild-to-severe loss of kidney function (estimated GFR 30-59 mL/min).
  – Stage 4: Severe loss of kidney function (estimated GFR 15-29 mL/min).
  – Stage 5: Kidney failure requiring dialysis or transplant for survival. Also known as ESRD (estimated GFR <15 mL/min)

Prevalence of CKD

• The overall prevalence of CKD in the general population is approximately 14 percent.
• More than 661,000 Americans have kidney failure. Of these, 468,000 individuals are on dialysis, and roughly 193,000 live with a functioning kidney transplant.

Prevalence of Anemia Increases as GFR Declines

<table>
<thead>
<tr>
<th>GFR*</th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 60</td>
<td>21.6%</td>
</tr>
<tr>
<td>≥ 30 to &lt; 60</td>
<td>5.6%</td>
</tr>
<tr>
<td>≥ 15 to &lt; 30</td>
<td>41.6%</td>
</tr>
<tr>
<td>&lt; 15</td>
<td>48.3%</td>
</tr>
</tbody>
</table>

*GFR = mL/min/1.73m².

Anemia Due to Chronic Kidney Disease (CKD) Is a Health Concern and Affects Hospital Systems

- Patients with CKD and anemia incurred higher annual direct health care costs compared to those without anemia (US claims data 1999-2001).1
- Medical costs for anemic patients were as much as twice those for non-anemic patients with the same comorbid conditions (US claims data 1998-2001).2
- Dialysis patients are hospitalized an average of twice per year.3
- Hospitalizations were associated with a decline in Hb levels among patients on dialysis4 – Hb levels should rise as events resolve4 – ≥2 months may be required to return to baseline Hb4


Definition of Anemia

- “A patient has an anemia whenever the hemoglobin level or the number of circulating red blood cells is reduced”

Pathogenesis

- Loss of RBC
  - Bleeding (e.g. menstrual or GI tract, HD)
- Excessive destruction of RBC
  - Hemolysis: sepsis, antibodies, drugs, prosthetic valves
  - Decreased red cell survival: hereditary disorders
- Poor, insufficient, or abnormal red blood cell production
  - Increased cytokine production (malignancies, dialysis, infection and inflammation)
  - Bone marrow infiltration
  - Inadequate iron intake or iron stores
  - Decreased erythropoietin production (CKD)

Anemia as a Complication of Other Diseases

- NDD-CKD (Non-dialysis dependent)
- Hemodialysis
- Peritoneal Dialysis
- HIV
- Malignancy
- Multiple System Failure (ICU patients)
- Inflammatory diseases (IBD, RA, SLE)
- Anemia of Pregnancy/Postpartum/Uterine Bleeding

Pathophysiology of Anemia Due to CKD: Erythropoietin Deficiency

- Erythropoietin Deficiency
- Hypoxia
- Increased O2-Carrying Capacity
- Bone Marrow
- RBCs

RBCs = red blood cells.

Pathophysiology of Anemia Due to CKD: Erythropoietin Deficiency

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- Erythropoietin Deficiency
- Bone Marrow
- Increased O2-Carrying Capacity
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Causes of Anemia in Hemodialysis Patients
- Decreased endogenous erythropoietin
- Blood sampling
- Dialyzer blood loss
- Occult bleeding
- Reduced RBC survival
- Dietary iron deficiency
- Bone marrow suppression
- Vitamin deficiencies
  - Malnutrition (malabsorption)

Symptoms and Consequences of Anemia

**Symptoms**
- Fatigue
- Shortness of breath
- Impaired exercise tolerance
- Lightheadedness
- Difficulty concentrating
- Pale skin
- Tachycardia

**Consequences**
- Decreased quality of life
- Decreased exercise tolerance
- Reduced cardiac workload
- Worsened LVH, CHF
- Reduced mentation
- Increased hospitalization
- Increased mortality

Mortality Risk

- Compared to patients who had no known co-morbidity, patients with DM had a 50% increased risk of death
- Anemia and CKD were independently associated with a 100% increased risk of death
- Mortality risk was further increased in patients who had multiple co-morbidities with anemia being a significant multiplier of mortality risk

- DM: Relative risk 1.5
- Anemia: Relative risk 2.0
- CKD: Relative risk 2.0
- DM and Anemia: Relative risk 2.4
- DM and CKD: Relative risk 2.4
- DM, Anemia, and CKD: 3.6


Laboratory tests and monitoring parameters used to evaluate anemia

- Hb response to an ESA takes between 2 and 6 weeks

- About 8 Days
- About 26 Days

- IMPAIRED KIDNEY FUNCTION IN PATIENTS WITH CKD LEADS TO DECREASED ERYTHROPOIETIN PRODUCTION

RBCs = red blood cells.
Hemoglobin and CKD

• Hemoglobin (Hb) testing should be carried out in all patients with CKD, regardless of stage or cause.

• Diagnosis of anemia should be made and further evaluation should be undertaken at the following Hb concentrations:
  – < 13.5 gm/dL in males; < 12.0 gm/dL in females

• Lower limit of Hb: In patients with CKD, Hb should be 11.0 gm/dL or greater. (MODERATELY STRONG RECOMMENDATION)

• Upper limit of Hb: there is insufficient evidence to recommend routinely maintaining Hb levels at 13.0 gm/dL or greater in ESA-treated patients

Anemia Indices: Hemoglobin (Hb) vs Hematocrit (Hct)

• Severity of anemia is assessed best by measuring Hb concentration rather than Hct

• Hb is a stable analyte that is measured directly.

• The Hb assay is standardized and is not influenced by differences in instrumentation

• Hct measurement is relatively unstable and lacks standardization.

• Hct result is derived indirectly by automated analyzers and is instrumentation dependent

• Hct increases with storage temperature and duration because stored red blood cells swell

Iron Indices

• TSAT
  – Iron availability for transport to bone marrow for incorporation into heme
  – % transferrin saturated with iron
  – (serum iron/TIBC) x 100
  – Normal range 20-50%
  – Lower limit ≥ 20%

• Ferritin
  – Index of total iron stores
  – Normal range 12-300 ng/mL
  – HD patients: Target 200 – 500 ng/mL (previously 800 ng/mL)
  – Non dialysis (ND) or peritoneal dialysis (PD) patients: Target 100 – 500 ng/mL (previously 800 ng/mL)

Iron Deficiency in CKD and HD

• Blood losses are usually high

• In patients using erythropoietic stimulating agents (ESA) therapy, assuring adequate iron stores in order to support erythropoiesis is critical

• Oral iron usually can not maintain adequate iron stores, especially in patients receiving (ESA)

• Prevention of functional and absolute iron deficiency by regular use of IV iron improves sensitivity to ESA

Functional vs Absolute Iron Deficiency Anemia

• Functional Iron Deficiency
  – Iron stores can not be mobilized quickly enough for production of new RBCs
  – Ferritin: ≥ 100 ng/mL
  – TSAT< 20%

• Absolute Iron Deficiency
  – Iron stores are depleted or are too low to support normal hemoglobin or RBCs
  – Ferritin < 100 ng/mL
  – TSAT < 20%

Therapies used in the management of anemia in patients with CKD
History of Anemia Management

- 1600s animal blood was transfused into humans
- 1800s bloodletting was common
- 1900 – 1900 patient-to-patient transfusion
- 1940 Rh factors first described
- 1990 blood substitutes, Epogen®
- 2007 Mircera®
- 2001 Aranesp®

Erythropoietin Stimulating Agents (ESAs)

- Epoetin alfa (Procrit®, Epogen®)
- Darbepoetin alfa (Aranesp®)
- ESAs stimulate the bone marrow to produce red blood cells

Epoetin alfa (Procrit®, Epogen®)

- The recommended starting dose for adult patients is 50 to 100 Units/kg 3 times weekly intravenously or subcutaneously
- The intravenous route is recommended for patients on hemodialysis.

Darbepoetin alfa (Aranesp®)

- CKD patients on dialysis
  - The recommended starting dose is 0.45 mcg/kg intravenously or subcutaneously once every 2 weeks as appropriate.
  - The intravenous route is recommended for patients on hemodialysis.

- CKD patients not on dialysis
  - The recommended starting dose is 0.45 mcg/kg body weight intravenously or subcutaneously given once at four week intervals as appropriate.

Darbepoetin alfa (Aranesp®)

<table>
<thead>
<tr>
<th>Previous epoetin alfa dose (Units/week)</th>
<th>Aranesp® adult starting dose (mcg/week)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1,500</td>
<td>6.25</td>
</tr>
<tr>
<td>1,500 to 2,499</td>
<td>6.25</td>
</tr>
<tr>
<td>2,500 to 4,999</td>
<td>12.5</td>
</tr>
<tr>
<td>5,000 to 10,999</td>
<td>25</td>
</tr>
<tr>
<td>11,000 to 17,999</td>
<td>40</td>
</tr>
<tr>
<td>18,000 to 33,999</td>
<td>60</td>
</tr>
<tr>
<td>34,000 to 89,999</td>
<td>100</td>
</tr>
<tr>
<td>≥ 90,000</td>
<td>200</td>
</tr>
</tbody>
</table>

Warnings

- ESAs increase the risk of death, myocardial infarction, stroke, venous thromboembolism, thrombosis of vascular access and tumor progression or recurrence.
- Initiate ESA treatment when the hemoglobin level is less than 10 g/dL.

https://www.fda.gov/Drugs/DrugSafety/ucm259639.htm

Package Inserts:
- Epoetin alfa (Procrit®, Epogen®)
- Darbepoetin alfa (Aranesp®)
Warnings

- In controlled trials, patients experienced greater risks for death, serious adverse cardiovascular reactions, and stroke when administered 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 dose sufficient to reduce the need for RBC transfusions

Utilization of Iron During Erythropoiesis

- During therapy with ESA, rate of erythropoiesis increases 2-3 fold
- Iron moves from reticuloendothelial cells to erythroid marrow
- May result in absolute iron deficiency
- Diminished availability of iron to erythrocyte precursors is most significant mechanism for inadequate response to therapy

Iron therapy can be given in two formulations

- Oral iron
- Intravenous iron

Choice Between Oral vs Intravenous Formulations

- Acuity of the anemia
- Costs
- Availability of different iron replacement products
- Ability of the patient to tolerate oral iron preparation
- Most patients are treated with oral iron because it is generally effective, readily available, inexpensive, and safe.
- However, up to 70 percent of patients for whom oral iron is prescribed report gastrointestinal side effects

Current available Oral Iron Formulations in the US

<table>
<thead>
<tr>
<th>Agent</th>
<th>Amount of elemental iron</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferrous Fumarate</td>
<td>contains 33% elemental iron per mg of mineral salt</td>
</tr>
<tr>
<td>Ferrous Gluconate</td>
<td>contains approximately 10 to 14% elemental iron per mg of mineral salt</td>
</tr>
<tr>
<td>Ferrous Sulfate</td>
<td>generally contains 20 to 30% elemental iron per mg of mineral salt, but can vary by manufacturer</td>
</tr>
<tr>
<td>Polysaccharide Iron Complex</td>
<td>The number in the name is the mg of elemental iron (eg, NovaFerrum 50 contains 50 mg elemental iron per capsule)</td>
</tr>
</tbody>
</table>

Causes of Failure of Oral Iron

- Non adherence
- GI Disturbances
- Iron malabsorption
Issues to Consider

Causes of Failure of Oral Iron
- Non-adherence
- GI Disturbances
- Iron malabsorption

Causes of Failure of IV Iron
- Anaphylaxis
- Hypersensitivity reaction

Uses for IV Iron
- Patients who cannot (or prefer not to) tolerate the gastrointestinal side effects of oral iron.
- Patients who prefer to replete iron stores in one or two visits rather than over the course of several months.
- Ongoing blood loss that exceeds the capacity of oral iron to meet needs (e.g., heavy uterine bleeding)
- Anatomic or physiologic condition that interferes with oral iron absorption.
- Coexisting inflammatory state that interferes with iron homeostasis.
- Patients receiving supplemental ESA therapy

Approved Dosing Guidelines

<table>
<thead>
<tr>
<th>Agent</th>
<th>IV Push</th>
<th>IV Infusion</th>
<th>Total Repletion Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium ferric gluconate (Ferrlecit)</td>
<td>125 mg over 10 min</td>
<td>125 mg/100 mL over 1 hour</td>
<td>1 gram</td>
</tr>
<tr>
<td>Iron sucrose (Venofer)</td>
<td>100 – 200 mg over 2-5 min</td>
<td>100 – 400 mg infusion</td>
<td>1 gram</td>
</tr>
<tr>
<td>Iron dextran</td>
<td>100 mg over 2 min</td>
<td>Not FDA approved</td>
<td>1 gram</td>
</tr>
<tr>
<td>Ferumoxytol (Feraheme)</td>
<td>Not available</td>
<td>510 mg in 50-200 mL over at least 15 min</td>
<td>1 gram</td>
</tr>
<tr>
<td>Ferric carboxymaltose (Injectafer)</td>
<td>750 mg, IVP at 100 mg/min</td>
<td>750 mg in no more than 250 mL over 15 min</td>
<td>1500 mg</td>
</tr>
</tbody>
</table>

Patient Case

- A 65-year-old man with stage 3 CKD presents to the nephrology office. He has a 7-year history of type 2 diabetes and presents with a foot ulcer. Hemoglobin level (Hb) is 8.4 g/dL, serum ferritin level is 87 ng/mL, and TSAT is 15%.

- Would you immediately begin ESA therapy?

Role of Pharmacist’s in Anemia Management

- Appropriate initiation, titration, and discontinuation of ESA
- Evaluate appropriateness of oral versus intravenous iron agents in CKD patients
- Monitor for adverse reactions
- Monitor markers of efficacy: Hb, TSAT, Ferritin
- Follow-up Medication Use Evaluations to monitor outcomes and adherence with guidelines

Patient Case

- A 67-year-old man with stage 3 CKD presents to the nephrology office for routine follow-up. He reports feeling fatigued, but denies other specific complaints. He brings labs which were recently collected at his primary care physician's office to the visit, which show a hemoglobin of 8.0 gm/dL, TSAT 25%, serum ferritin 200 ng/mL.

- Would you begin ESA therapy as first line treatment?
Thank you

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