

Anemia Fact Sheet

Anemia is a decreased concentration of hemoglobin (Hgb) that leads to reduced oxygen-carrying capacity in the blood (Brown & Gilliland, 2020). “For practical purposes, anemia is considered when one or more of the following are decreased: hemoglobin concentration, hematocrit, or RBC count,” (Colbert et al., 2020a, para. 1). Anemia is usually categorized as normocytic normochromic due to a decrease in the production of erythropoietin (EPO) and a decrease in the lifespan of red blood cells (Brown & Gilliland, 2020). EPO is a circulating hormone – 90% of which is produced in the kidneys and the remainder in the liver.

Healthy kidneys produce EPO in response to hypoxia. EPO stimulates the erythroid progenitor cells in the bone marrow; reticulocytes are released from the bone marrow into the bloodstream, and they mature into red blood cells. The 10% of EPO produced by the liver is enough to trigger the production of about only one-third of the red blood cells required by the body, resulting in anemia.

Anemia may arise as a complication of chronic kidney disease (CKD). When kidneys fail, less EPO is produced which results in a decrease in the availability and production of red blood cells; Therefore, the risk of anemia increases with a decline in kidney function and is frequently seen in CKD stages 3 to 5 (Batchelor et al., 2020). Yet, the severity of anemia of CKD is directly related to the degree of loss of kidney function. In individuals with advanced stages of CKD, the etiology of anemia tends to be multifactorial and includes the following:

- Inadequate EPO production.
- Shortened red blood cell survival time (40%-60% of normal) because of uremia and other toxins.
- Blood loss from the hemodialysis procedure, frequent lab draw, and gastrointestinal blood loss.
- Iron deficiency.
- Deficiency of water-soluble vitamins (e.g., vitamin B12 and folate). (Batchelor et al., 2020).

Symptoms of anemia include pallor, fatigue, shortness of breath, decreased cognition, muscle weakness, decreased exercise tolerance, chest pain, tachycardia, and a decreased quality of life. Anemia contributes to the development of left ventricular hypertrophy, cardiomyopathy, congestive heart failure, and ischemic heart disease. Cardiovascular disease and CKD stage 5 place this population at increased risk of morbidity and mortality.

Treatment

Erythropoiesis-Stimulating Agents (ESAs)

Recommendations have been given from the U.S. Food and Drug Administration (FDA) (2017) to use the lowest dose of ESAs sufficient to reduce the need for red blood cell transfusions for each patient and adjust the dose as appropriate. Initiation of therapy begins when the Hgb is < 10.0 g/dL. “Healthcare professionals should weigh the possible benefits of using ESAs to decrease the need for red blood cell transfusions in CKD patients against the increased risks for serious cardiovascular events, and should inform their patients of the current understanding of potential risks and benefits,” (FDA, 2017, para. 3).

ESAs are used to treat anemia in patients with chronic kidney disease. The FDA has approved epoetin alfa (Epogen®), darbepoetin alfa (Aranesp®), and methoxy polyethylene glycol-epoetin beta (MIRCERA®) for use in patients on dialysis. These agents are dosed based on the patient’s weight (Amgen Manufacturing, Ltd. 2018; 2019; Vifor Pharma Group, 2020).

Epoetin alfa (Epogen):

- Starting dosage: Adults 50-100 U/kg.
- Administer intravenous or subcutaneous three times weekly.

Darbepoetin alfa (Aranesp):

- Starting dosage: Adults 0.45 mcg/kg.
- Administer intravenous or subcutaneously weekly or 0.75 mcg/kg every 2 weeks.

Methoxy polyethylene glycol-Epoetin beta (Mircera):

- Starting dose 0.6 mcg/kg.
- Administer intravenous or subcutaneous once every 2 weeks.
- Administer monthly once Hgb has stabilized.

“The use of ESAs can increase the risk for stroke, heart attack, heart failure, blood clots, and death,” (FDA, 2017, para. 6). Most hemodialysis patients will require intravenous iron supplementation while receiving ESAs. Iron stores may be used up quickly once treatment with ESAs begins. Many dialysis providers use an algorithm/protocol to dose ESAs and administer intravenous iron. An anemia manager – usually a registered nurse – applies the algorithm/protocol based on the laboratory values of the individual patient, consulting with the patient’s nephrologist as necessary.

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Iron is essential for Hgb formation. Kidney Disease Improving Global Outcomes (KDIGO) (2012) guidelines recommend a trial of iron repletion if the serum ferritin is < 500 with a transferrin saturation (TSAT) < 30%. Current guidelines recommend against using iron products with the ferritin is 500 ng/mL or greater.

The studies on ESA use in anemia of CKD and the FDA actions have been followed by a change in clinical practice. Between 2006 and 2015, CKD patients in the United States were increasingly less likely to be treated with ESAs and more likely to receive intravenous iron supplementation and blood transfusions (Park et al., 2018).

For patients with CKD on dialysis who require iron supplementation, intravenous iron is generally recommended, as intravenous iron consistently achieves higher TSAT and ferritin values than oral iron. Examples of iron replacement therapies and routes include the following:

- **Intravenously:**
 - Iron dextran complex (Dexferrum, INFeD).
 - Iron sucrose (Venofer).
 - Ferric carboxymaltose (Injectafer).
 - Ferumoxytol (Feraheme).
- **Orally:**
 - Auryxia (Ferric Citrate).
 - Accrufer (ferric Maltol).
- **Liquid Bicarb:**
 - Triferic (a soluble iron replacement therapy added to the hemodialysis solution).

An alternative to ESAs is the use of agents that stimulate endogenous EPO production in renal tissues. "HIF-PH inhibitors improve iron mobilization to the bone marrow and induce considerably lower but more consistent blood erythropoietin levels than ESAs. They also promote erythroferone production by erythroblasts which reduces hepcidin interference, allowing for greater utilization of iron," Colbert et al., 2020b, para. 36). An advantage of these agents is that they are administered orally. Four HIP-PH inhibitors currently under development are:

- Roxadustat.
- Vadadustat.
- Daprodustat.
- Molidustat.

Lab Testing

The following targets are recommended by KDIGO (2012) for patients with stage 5 CKD on dialysis:

- TSAT > 20%, no upper limit specified.
- Ferritin lower limits:
 - For CKD G5 treated by KRT: 200 ng/mL.
 - For CKD without KRT: 100 ng/mL.
 - 500 ng/mL not routinely recommended.
- Serum B12 and folate levels.

Nonresponse to EPO

About 90% of persons given ESAs will respond with an increase in circulating red blood cells. There are several reasons why an individual does not respond to treatment. Among them are:

- **Inadequate EPO dose:**
 - Hgb below target in the absence of causes of non-response.
 - Low Epogen based on body weight, inappropriately missed or held doses, frequent dose changes, and non-compliance.
- **Iron deficiency – Absolute and functional:**
 - Absolute iron deficiency may be caused by blood loss and/or not receiving enough iron. Lab values that indicate absolute iron deficiency include TSAT < 20% and ferritin < 200ng/mL
 - Functional iron deficiency occurs when iron is mobilized slowly from the reticuloendothelial system to keep up with the demands of ESA-driven erythropoiesis. Total iron-binding capacity is generally normal to elevated. Intravenous iron will correct.
- **Infection and inflammation:**
 - Inflammatory iron blockade results in iron being blocked from leaving the reticuloendothelial system due to an infection or inflammation. The total iron binding capacity may be reduced.
 - Known acute or chronic infections or inflammatory processes, including access infection, AIDS, rheumatologic disorders, surgical inflammation, dental disease, and cancer.
 - Labs indicating infection/inflammation include elevated ferritin and decreased TSAT, elevated white blood cells, and significantly elevated C-reactive protein (also called acute phase reactant).
- **Blood loss:**
 - Excessive blood loss from gastrointestinal bleed, phlebotomy, hemodialysis, or other sources.

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- **Secondary hyperparathyroidism:**
 - Causes marrow fibrosis aggravating anemia.
 - Documented disease, bone changes, iPTH 300 pg/mL.
- **Aluminum toxicity:**
 - Interferes with iron incorporation into Hgb and also disturbs human erythropoiesis.
 - Develop deposits in the bone marrow and may cause microcytic anemia.
- **Co-morbid condition:**
 - Malignancies, hematologic disorders, AIDS, pregnancy, chemotherapy.
- **Hemolysis:**
 - Destruction of red blood cells caused by a mechanical problem, medication, or sterilant. Labs will show an acute decrease in Hgb.
- **Hypoalbuminemia:**
 - Detected by lower protein intake than the recommended level. Labs show a decreased serum albumin.
 - Vitamin deficiencies, vitamin B-12 deficiency, or folate deficiency.
 - Pure red cell aplasia or anti-erythropoietin antibody-associated anemia.
- **Intervention:**
 - Treat anemia based on the most current evidence.
 - Initiate any future anemia work-up and order laboratory and/or diagnostic tests as appropriate.
 - Adjust medication based on patient's response.
 - Evaluate the patient for any comorbid conditions (i.e., pulmonary disease, angina congestive heart failure, cerebrovascular disease) and collaborate with a healthcare provider as appropriate.
 - Assess for concomitant prescriptions that interfere with oral iron absorption.
 - Consult with hematology/oncology if the cause of non-response is not evident. (Brown & Gilliland, 2020, p. 329-332).

If a patient does not respond to ESA administration, evaluate for the above response. Iron deficiency is a significant cause because iron stores may be depleted quickly once ESA therapy is initiated. Identify and treat the underlying source of nonresponse; the ESA dosage may need to be adjusted to prevent worsening anemia. Once the cause of nonresponse is resolved, change the ESA to prevent Hgb from exceeding the recommended range.

Advance Practice Nursing Care

In addition to the items outlined above:

- **Assessment:**
 - Assess for signs and symptoms of anemia (e.g., angina, hypotension, fatigue, and shortness of breath).
 - Interpret results of any diagnostic test, studies, or laboratory values.
 - Initiate anemia work-up per current evidence-based research, guidelines, or per facility protocol.
 - Monitor patient's ability to follow their response to the treatment plan.
 - Monitor for any potential causes of non-response to anemia management.

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