Treatment Issues in Anemia of Chronic Kidney Disease

Wissam Saliba, MD, Samer Antonios, MD, and Joseph Abdallah, MD

Abstract

- **Objective:** To review the pathophysiology and approach to management of chronic kidney disease (CKD)–related anemia.
- **Methods:** Review of the literature.
- **Results:** CKD is an increasingly common medical condition in the United States. It is associated with a myriad of complications, among which anemia is perhaps the most treatable. Anemia has a high impact on the morbidity and mortality of patients with CKD, mainly by inducing left ventricular hypertrophy. CKD-related anemia is primarily due to erythropoietin insufficiency, but absolute and functional iron deficiency, iron restriction, and erythropoietin resistance are also factors. In recent years, hepcidin has emerged as an important player in iron homeostasis and the pathophysiology of iron restriction and represents a potential target for future therapeutic approaches. Early diagnosis and evaluation of anemia are fundamental in the management of patients with CKD and should include iron status assessment. Treatment relies on a combination of erythropoietin and iron supplementation, but the optimal hemoglobin target and threshold at which to treat are still debated.
- **Conclusion:** Effective treatment of CKD-related anemia can reduce cardiovascular complications, slow progression of renal failure, and improve quality of life.

The prevalence of end-stage renal disease (ESRD) in the United States is increasing. Currently, about 600,000 patients have ESRD, and this number is expected to reach 750,000 by 2015 [1]. This coincides with an increase in the prevalence of chronic kidney disease (CKD), notably stage 3. In 2003, 19.1 million Americans had CKD (about 11% of the population) [2]. Current classification of CKD includes parenchymal damage for stages 1 and 2 and decrease of glomerular filtration rate (GFR) regardless of parenchymal damage for stages 3 and higher [3] (Table 1). The significant number of CKD patients imposes a high cost burden on the health care system.

One of the most challenging problems in this patient population is anemia. CKD-related anemia is defined by the National Kidney Foundation (NKF) as a hemoglobin (Hb) level of less than 13.5 g/dL in males and less than 12 g/dL in females [4]. The National Health and Nutrition Examination Surveys from 1999 to 2002 reported that anemia was more common in females, African Americans, older patients (notably age > 70 years), and patients with CKD stages 3 and above [5]. It is well known that anemia develops earlier in diabetic patients with CKD. About 68% of stage 4 CKD patients with diabetes mellitus have anemia, but only about 34% of stage 4 CKD nondiabetic patients are anemic [6]. In this article, we review the pathophysiology and causes of anemia related to CKD and provide a systematic approach for its management.

Pathophysiology

Normal Erythropoiesis

Understanding normal erythropoiesis helps elucidate the pathophysiology of CKD-related anemia. Healthy red blood cell (RBC) production requires both erythropoietin (EPO) and iron [7]. EPO production by the kidney increases with cell hypoxia. EPO works early in the cycle of RBC maturation by stimulating the erythroid burst-forming units and colony-forming units. In contrast, iron is required later in the cycle for the transformation of erythroblasts into reticulocytes.

The average human body contains about 4 g of iron, distributed between the hemoglobin (2.4 g) and the reticuloendothelial system (1 g). Around 20 mg of iron flow into the plasma pool daily from destruction of senescent RBCs and are used by the bone marrow for production of new erythrocytes. In contrast, only about 1 to 2 mg of iron are absorbed every day in the proximal duodenum to replace the iron lost through desquamation of intestinal mucosa cells [8]. Human physiology does not allow iron excretion. Iron absorption is the sole mechanism by which iron stores are physiologically controlled [9]. Unfortunately, the mechanism of intestinal iron absorption and its regulation are poorly understood.
Human cells can take up iron through different mechanisms [10] (Figure 1). Most cells use the transferrin receptor for uptake of iron in the form of iron-saturated transferrin. Other cells use the divalent metal transporter 1 (DMT1) for uptake of free iron. Macrophages use the iron provided by phagocytosis of senescent RBCs. The majority of cells use iron for their own purposes, such as synthesis of hemoglobin, enzymes, and other proteins. However, few cells are specialized iron exporters; these include the duodenal enterocytes, hepatocytes, macrophages, and embryonic or placental cells. Despite the various mechanisms for iron uptake, iron-exporting cells have only one way to export iron: a 12 transmembrane-segment protein called ferroportin [11]. Ferroportin is the only known iron-exporter in vertebrates. It is inhibited by hepcidin, currently considered as the master of iron homeostasis.

Hepcidin was discovered in 2000. It is a small peptide hormone produced by the liver (Hep-) and has bactericidal properties (-cidin). Rivera et al [12] showed that mice that were intraperitoneally injected with hepcidin acquired extremely low plasma iron level for up to 48 hours after injection. Hepcidin binds to ferroportin in iron-exporting cells and causes its internalization and destruction, preventing the efflux of iron into the plasma iron pool. Therefore, when stimulated by hepcidin, the enterocytes, the hepatocytes and the macrophages cannot export iron. Hepcidin itself is stimulated by inflammatory states and iron load and inhibited by erythropoietic signals [13] (Figure 2).

### Erythropoiesis in Renal Failure

As the kidney function declines, the diseased kidneys become unable to produce sufficient quantities of erythropoietin. EPO deficiency is well documented in CKD patients [14], but its magnitude does not appear to be related to the level of kidney function. Anemia of CKD is multifactorial. Although true EPO deficiency is present in most patients with CKD, several other factors contribute to the anemia:

**Reticulo-endothelial blockade.** It is well known that CKD is a low-grade chronic inflammatory state due to imbalance of pro-oxidants and antioxidants [15]. Markers of inflammation such as C-reactive protein and interleukin-6 levels are often elevated. This leads to stimulation of hepcidin production by the hepatocytes. The decreased renal clearance of hepcidin due to failing kidneys increases its serum level even further. This increase in hepcidin levels causes EPO resistance and iron restriction, as explained above. This is often referred to as reticulo-endothelial blockade.

**Absolute iron deficiency.** Absolute iron deficiency is often present in patients initiating hemodialysis, and replenishing iron stores is crucial in the management of their anemia. Absolute iron deficiency develops in CKD patients due to multiple factors including decrease in intestinal absorption of iron, occult gastrointestinal bleeding due to platelet malfunction and increased incidence of arterio-venous malformation, and blood loss from repetitive laboratory testing. Furthermore, the initiation of erythropoietin-stimulating agents (ESA) requires large amounts of stored iron [16]. In fact, raising Hb from 10 g/dL to 13 g/dL requires the formation of 150 g of Hb (estimated total blood volume = 5 L). Since Hb is 0.34% iron, the formation of 150 g of Hb would require 510 mg of iron, which is more than half of the iron stored in the reticulo-endothelial system.

**Functional iron deficiency.** Functional iron deficiency or ineffective erythropoiesis is characterized by the presence of adequate iron stores but a slow iron mobilization rate into the site of erythropoiesis when ESA is started. In other terms, iron transporters fail to keep up with the increased rate of erythropoiesis. It is particularly important to differentiate

### Table 1. Stages of Chronic Kidney Disease

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>GFR (mL/min/1.73 m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Kidney damage with normal/increased GFR</td>
<td>≥ 90</td>
</tr>
<tr>
<td>2</td>
<td>Kidney damage with mild decrease in GFR</td>
<td>60–89</td>
</tr>
<tr>
<td>3</td>
<td>Moderate decrease in GFR</td>
<td>30–59</td>
</tr>
<tr>
<td>4</td>
<td>Severe decrease in GFR</td>
<td>15–29</td>
</tr>
<tr>
<td>5</td>
<td>Kidney failure</td>
<td>&lt; 15</td>
</tr>
</tbody>
</table>

GFR = glomerular filtration rate. (Adapted with permission from the National Kidney Foundation.)

### Figure 1. Mechanisms of iron uptake. DMT1 = divalent metal transporter 1; TfR = transferring receptor.

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between functional iron deficiency and iron restriction through reticulo-endothelial blockade, as the former is responsive to iron therapy while the latter is not. This will be discussed later in the article.

Other factors may contribute to CKD-related anemia such as the presence of uremic inhibitors, vitamin B₁₂ or folic acid deficiency, and reduced RBC life.

Outcomes
Anemia is associated with an increase in mortality and morbidity of patients with CKD. Symptoms are similar to those found in the normal population and include anorexia, fatigue, decreased cognition and mental acuity, sleep disturbances, increased risk of hospitalization, and prolonged hospital length of stay. In addition, anemia is an important cause of left ventricular hypertrophy (LVH) and congestive heart failure due to hypoxia and increased heart strain [17]. A decrease of Hb by 1 mg/dL may cause a 20% to 40% increase in left ventricular dilatation. LVH may develop in patients with Hb levels as low as 12 mg/dL. Moreover, Mohanram et al [18] identified anemia as an independent risk factor for progression of diabetic nephropathy to ESRD, with an adjusted hazard ratio of 1.99 in patients with Hb < 11.3 g/dL.

Evaluation
According to the Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines [4], anemia screening should be done in all patients with CKD regardless of stage or etiology. Hb levels should be measured at least annually. The evaluation of patients with anemia and CKD should include measurement of RBC indices, reticulocyte count, fecal occult blood test, and assessment of iron status.

Iron management is a key to successful anemia treatment, because it has been shown to increase Hb level and decrease EPO resistance and EPO dose. In fact, the addition of iron to EPO therapy was associated with a net saving of $1390 per 1 g/dL increase in Hb over a 12-week period [19]. Ferritin and transferrin saturation (TSAT) are the most widely used iron markers. Both are easy to use, of moderate cost, and widely available. However, they have a high variability and a poor accuracy.

Ferritin
Ferritin provides an indirect measure of the iron stored in the reticulo-endothelial system. In patients with no CKD, a ferritin level < 15 ng/mL is indicative of iron deficiency anemia. Ferritin is also an intense positive acute phase reactant. In CKD patients or patients with inflammatory or infectious conditions, a ferritin level up to 600 ng/mL may be present in the setting of iron deficiency anemia. This has actually been illustrated in several studies where the sensitivity of ferritin for iron deficiency anemia in CKD patients was less than 50% [20,21]. However, the same studies showed a very high specificity. This means that iron deficiency anemia is almost always present in patients with low ferritin level.

TSAT
Transferrin saturation is calculated as the plasma iron level divided by total iron binding capacity (TIBC). It provides a measure of circulating iron. TSAT has poor to moderate accuracy as well due to the high variability of serum iron. In addition, TIBC is a negative acute phase reactant and its level decreases in inflammatory conditions. It is also affected by nutritional status and may be low in patients with malnutrition.

Several newer tests are currently available. The reticulocyte Hb content (CHR) test provides a direct measure of iron at the level of reticulocytes. Several studies have shown CHR to be a more stable and more sensitive marker of iron deficiency than ferritin or transferrin in EPO-treated hemodialysis patients [22]. However, the clinical utility of CHR in patients with CKD has not been established. Other tests such as percentage of hypochromic RBCs and soluble transferring receptor are still investigational and their use in CKD patients is not yet indicated. A hepcidin level may potentially be useful in iron management in CKD patients [23]. Theoretically, it may distinguish between reticulo-endothelial blockade (high hepcidin level) and functional

![Figure 2. Regulation of iron level by hepcidin.](image-url)
**ANEMIA IN CKD**

**Table 2. Oral Iron Preparations**

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Pills Required to Provide 200 mg Iron, n</th>
<th>Tablet Size, mg</th>
<th>Elemental Iron per Pill, mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferrous sulfate</td>
<td>3</td>
<td>325</td>
<td>65</td>
</tr>
<tr>
<td>Ferrous gluconate</td>
<td>6</td>
<td>325</td>
<td>35</td>
</tr>
<tr>
<td>Ferrous fumarate</td>
<td>2</td>
<td>325</td>
<td>108</td>
</tr>
<tr>
<td>Iron polysaccharide</td>
<td>2</td>
<td>150</td>
<td>150</td>
</tr>
</tbody>
</table>

Adapted with permission from the National Kidney Foundation.

Iron deficiency anemia (low hepcidin level), which is one of the most challenging conditions in iron status assessment. However, only limited data are currently available and more studies are needed to assess the clinical utility of this test.

**Management**

Previously, RBC transfusion and androgen therapy were the only options for anemic CKD patients. The U.S. Food and Drug Administration (FDA) approval of EPO revolutionized management. However, the timing of the treatment, the Hb target, the TSAT/ferritin targets and indications for RBC transfusions are still “hot topics” and recommendations change every year. Currently, the management of anemia of CKD is complex and consists of a combination of erythropoiesis-stimulating agents (ESA) and iron therapies.

**Erythropoiesis-Stimulating Agents**

The identification and cloning of the human erythropoietin gene led to the production of recombinant erythropoietin (EPO). It was approved by the FDA for treatment of anemia in ESRD patients in 1989. Shortly after, it was approved for CKD patients. Currently, 30% of predialysis patients use an ESA for anemia treatment. However, up to 65% of CKD patients have a Hb < 11 g/dL and may be eligible for ESA use [24]. The use of ESA has resulted in significant clinical benefits, including correction of anemia, decrease of the need for blood transfusions, improved quality of life and level of energy, decreased LVH, and possibly decreased mortality. ESA can be administered either intravenously (IV) or subcutaneously (SQ), and the dose may be given once weekly or less frequently. Recently, several studies have shown that the use of ESA in patients with active cancer may shorten survival and increase the risk of tumor growth. This was especially significant with head and neck cancer [25], metastatic breast cancer [26] and cervical cancer [27].

The 2 most commonly used ESAs in the United States are epoietin alfa and darbepoietin alfa. The latter is characterized by a 3-fold longer half-life and greater biological activity and may be administered less frequently than epoietin alfa. However, darbepoietin alfa is almost twice as expensive as epoietin alfa. In a study of 166 CKD patients randomly assigned to either epoietin alfa or darbepoietin alfa, Locatelli et al demonstrated no significant difference in mortality or safety profile [28].

Newer ESAs including continuous erythropoiesis receptor activator (CERA), hematide and hypoxia-inducible factor (HIF) stabilizers are not yet FDA-approved and their safety and clinical utility are still to be determined.

The K-DOQI guidelines regarding the use of ESA in CKD patients are as follows [4]:

- ESA may be administered subcutaneously in CKD patients, while IV administration is preferred in dialysis patients
- The less frequent administration of ESA is favored, particularly in CKD patients.

**Iron Preparations**

Iron assessment should always be done before the start of ESA therapy, and iron deficiency should be treated. Several oral and IV iron preparations are available in the United States (Table 2 and Table 3). Oral iron should be given between meals if tolerated, as its absorption may be lowered by food and antacids. The efficacy and safety of IV iron versus oral iron for treatment of CKD patients has been evaluated in several studies. A meta-analysis of 6 trials including anemic patients with CKD (not on hemodialysis) showed minimal advantages of IV iron but higher cost and more side effects [29]. Furthermore, recurrent infusions of IV iron in CKD patients jeopardize the future use of veins for arteriovenous fistulas. Side effects from IV iron formulations may include anaphylaxis, sepsis, renal injury, and iron toxicity. Ferumoxytol is an ultrasmall superparamagnetic iron oxide nanoparticle coated with a semi-synthetic carbohydrate and designed to minimize immunologic sensitivity [30]. It can be rapidly injected (510 mg over 17 seconds) and has fewer side effects than other iron preparations. It might be a newer alternative to traditional preparations. However, the clinical experience with ferumoxytol is still limited. In addition, ferumoxytol treatments are very costly.

The K-DOQI guidelines regarding the use of iron in CKD patients are as follows [4]:

- The route of administration of iron can be either oral or IV in patients with CKD (not on dialysis), while the IV route is preferred for patients on dialysis
- Iron status tests should be performed every month during initial ESA treatment, and every 3 months during stable ESA treatment
Timing of Treatment
The timing of treatment is a debatable topic. Studies have shown a clear association between anemia and LVH, but the level of Hb at which correction of the anemia can reverse LVH is still to be determined. This question was addressed in a meta-analysis of 15 studies involving 1731 CKD and ESRD patients treated by EPO examining left ventricular mass index (LVMI) changes with treatment [31]. In patients with severe anemia (Hb < 10 mg/dL), raising Hb to ≤ 12 g/dL was associated with a reduction of LVMI by an estimated effect size of 32.73 g/m². However, in patients with moderate anemia (Hb ≥ 10 mg/dL), ESA treatment was associated with nonsignificant changes in LVMI. ESA treatment is known to improve quality of life in patients with CKD. However, it may increase the thrombotic risks.

The K-DOQI guidelines did not specify a particular Hb level at which ESA therapy should be started but rather left it to be determined by the clinician based on balancing risks and benefits. A 2007 update of the K-DOQI guidelines stated that selection of the Hb level at which ESA therapy is initiated should include consideration of potential benefits (including improvement in quality of life and avoidance of transfusion) and potential harms (including the risk of life-threatening adverse events).

Hemoglobin Target
The Hb target is defined as the Hb value that is clinically optimal for each patient based upon the particular circumstances. It is a subject of debate between the FDA and practice guideline recommendations. The K-DOQI guidelines themselves are constantly changing each year because of conflicting results of new studies. The TREAT study, published in October 2009, will probably influence practice and new recommendations.

Several studies were done to assess the Hb target in patients with CKD who are not on dialysis. A number of small studies conducted in the 1980s often lacked placebo groups and supported the suggestion that ESA therapy to high Hb targets provides survival benefits. However, new randomized controlled trials have shown unexpected results.

In the Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) trial, 1432 patients with CKD and anaemia were randomized for ESA treatment to either a target Hb of 13.5 g/dL or 11.3 g/dL [32]. The high Hb group had a higher composite endpoint of death, myocardial infarction, stroke, and hospitalization for CHF compared with the low Hb group, with a hazard ratio of 1.34. The difference in composite endpoint was blamed on oscillation and rapid increase in Hb levels after using ESA as well as possible damage to endothelium and smooth muscle cells due to higher ESA dose. The CHOIR trial, however, had some limitations including more underlying comorbid conditions in the high Hb group and high withdrawal rate.

The Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta (CREATE) trial involved 603 CKD patients assigned to a normal (13–15 g/dL) or subnormal (10.5–11.5 g/dL) Hb range [33]. No difference in cardiovascular events, survival, LVH, or rate of CKD progression was seen between the 2 groups; however, the normal Hb range patients had a better quality of life.

The Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT) trial was the largest study done on anemic patients with CKD [34]. In this study involving 4038 patients with diabetes, CKD, and anemia, Pfeffer et al randomly assigned patients to either darbepoietin alfa with a target Hb of 13 g/dL or placebo with rescue darbepoietin alfa when the hemoglobin level falls below 9 g/dL. There was no significant difference between the 2 groups in the overall rates of the primary endpoints (of death or a cardiovascular event or of death or end-stage renal disease). Surprisingly, more strokes occurred in patients assigned to darbepoietin alfa, with a hazard ratio of 1.92. The TREAT study, however, showed decreased need for transfusion and modest improvement in patient-reported fatigue in the darbepoietin alfa group as compared with the placebo group.

In conclusion, the optimal Hb target is yet to be determined. What is clear for now is that higher Hb targets are not beneficial and potentially harmful. More conservative Hb targets (Hb < 12 g/dL) should be evaluated through well-designed randomized controlled studies. The 2006 K-DOQI guidelines were published before the ending of the 3 studies mentioned above. A 2007 update followed the CREATE and CHOIR trial [4]:

- Hb target in CKD patients should generally be between 11 and 12 g/dL
- Hb target should not exceed 13 g/dL

Targets of Ferritin/TSAT
Unfortunately, there are no randomized controlled trials on patients with CKD (not on dialysis). The current K-DOQI

### Table 3. Intravenous Iron Preparations

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Maximum Single Dose</th>
<th>Recommended Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron dextran</td>
<td>1000 mg</td>
<td>100 mg × 10 doses</td>
</tr>
<tr>
<td>Iron gluconate</td>
<td>125 mg</td>
<td>125 mg × 8 doses</td>
</tr>
<tr>
<td>Iron sucrose</td>
<td>100 mg</td>
<td>100 mg × 10 doses</td>
</tr>
<tr>
<td>Ferumoxytol</td>
<td>510 mg</td>
<td>510 mg × 2 doses</td>
</tr>
</tbody>
</table>

Adapted with permission from the National Kidney Foundation.
ANEMIA IN CKD

guidelines are extrapolated from studies conducted on dialysis patients and recommend targets that reflect a conservative estimation of efficacy [4]:

- Sufficient iron should be administered to maintain ferritin > 100 ng/mL and TSAT > 20% in patients with CKD
- Sufficient iron should be administered to maintain ferritin > 200 ng/mL and TSAT > 20% (or CHr > 29 pg/cell) in patients who are on dialysis

What if TSAT < 20% and Ferritin > 500 ng/mL?
This is a question of differentiating functional iron deficiency (where iron therapy is effective) and iron restriction from inflammation and increased hepcidin level (where iron therapy is not beneficial and may be harmful). The subject of upper level of ferritin was raised by the Dialysis Patients’ Response to IV Iron with Elevated Ferritin (DRIVE) trial [35]. It involved patients on hemodialysis with Hb < 11 g/dL, ferritin 500 to 1200 ng/mL, TSAT < 25%, and EPO dosage > 22,500 international units/wk. In the DRIVE trial, Coyne et al randomly assigned 134 participants to either IV ferric gluconate (× 8 doses) or placebo. There was a greater Hb increase in the IV iron group than in the control group, as well as a greater increase in ferritin and TSAT. Moreover, there was no significant difference in the adverse events between the 2 groups.

The lack of studies relating safety to a specific high ferritin level makes the answer to the above question again individualized and based on patient characteristics. The K-DOQI guidelines regarding this issue are as follows [4]:

- There is insufficient evidence to recommend routine administration of IV iron if ferritin > 500 ng/mL
- When ferritin > 500 ng/mL, decisions regarding IV iron administration should weigh ESA responsiveness, Hb and TSAT level, and the patient’s clinical status

In other terms, check patients for infection or other inflammatory conditions (where IV iron is harmful), check C-reactive protein, CHr (if available), Hb/EPO dose ratio, and consider IV iron in individualized patients.

Indications for Blood Transfusion
The packed red blood cells transfusion in CKD patients should be avoided as much as possible. It is well known that transfusions may induce the formation of antibodies to human leukocytes antigen (HLA) that can reduce the success of kidney transplantation in the future [36]. In addition, transfusions may cause hypervolemia and symptoms of congestive heart failure, particularly in elderly patients. The K-DOQI guidelines state that no single Hb level should justify or require transfusion [4]. Risks and benefits of transfusion therapy should be considered in individualized patients.

Summary and Recommendations
Anemia has been implicated in the symptoms, morbidity, and prognosis associated with reduced kidney function. The etiology of CKD-related anemia is multifactorial. In all CKD patients, complete blood count, mean corpuscular volume, reticulocyte count, vitamin B12, folate acid, ferritin, TSAT, and possibly CHr (if available) should be measured as part of anemia workup. Iron deficiency, if present, should be treated and its causes established. If Hb is less than 11 g/dL, ESA therapy initiation should be discussed with the patient with focus on potential risks and benefits. It appears from available data that higher Hb targets are not beneficial and potentially harmful. The current K-DOQI guidelines advise for a Hb target of 11 to 12 g/dL, without exceeding 13 g/dL. Laboratory testing should be repeated monthly until ESA dose is stable. Hb level and iron markers should be followed every 3 months during stable ESA treatment.

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References