Anemia in renal disease: Diagnosis and management

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A R T I C L E   I N F O

SUMMARY

Chronic kidney disease (CKD) is a widespread health problem in the world and anemia is a common complication. Anemia conveys significant risk for cardiovascular disease, faster progression of renal failure and decreased quality of life. Patients with CKD can have anemia for many reasons, including but not invariably their renal insufficiency. These patients require a thorough evaluation to identify and correct causes of anemia other than erythropoietin deficiency. The mainstay of treatment of anemia secondary to CKD has become erythropoiesis-stimulating agents (ESAs). The use of ESAs does carry risks and these agents need to be used judiciously. Iron deficiency often co-exists in this population and must be evaluated and treated. Correction of iron deficiency can improve anemia and reduce ESA requirements. Partial, but not complete, correction of anemia is associated with improved outcomes in patients with CKD.

Introduction

Chronic kidney disease (CKD) affects approximately 26 million adults in the United States and millions of others are at risk.1 CKD is associated with significant morbidity and mortality, and these patients face many other medical problems related to CKD. One of the major medical issues facing this population is anemia, which often develops early in the course of CKD and contributes to poor quality of life. It has been shown to be strongly predictive of adverse effects, including complications and death from cardiovascular causes.2 Prior to the availability of human recombinant erythropoietin, patients receiving chronic dialysis treatment frequently required blood transfusions, exposing them to iron overload, viral hepatitis and HIV, and increasing production of antibodies to human antigens which can severely limit transplantation options.

The introduction of recombinant human erythropoietin in the late 1980s drastically changed the treatment of anemia in patients with CKD. The benefits of anemia treatment in this population reach far beyond the improvement of fatigue and decreased physical activity to a broad spectrum of physiologic functions. Thus the presence of anemia should be sought, diagnosed, and treated early in patients with CKD. The optimal hemoglobin (Hb) targets are still controversial and studies defining these goals are ongoing. The costs of anemia management in the chronic kidney disease population are considerable and need to be considered along with the risks and benefits.

Pathophysiology of anemia in patients with CKD

Anemia is defined by the World Health Organization as a Hb concentration less than 13.0 g/dL in adult males and non-menstruating females and less than 12.0 g/dL in menstruating females.3 Anemia is a common problem in patients with CKD, and its incidence increases as glomerular filtration rate declines. Population studies such as the National Health and Nutrition Examination Survey (NHANES) by the National Institutes of Health and the Prevalence of Anemia in Early Renal Insufficiency (PAERI) study suggest that the incidence of anemia is less than 10% in CKD stages 1 and 2, 20–40% in CKD stage 3, 50–60% in CKD stage 4 and more than 70% in CKD stage 5.4,5

The cause of anemia in patients with CKD is multifactorial. The most well-known cause is inadequate erythropoietin (EPO) production, which is often compounded by iron deficiency. As renal failure progresses, the contribution of EPO deficiency to anemia increases. The role of decreased renal EPO synthesis in CKD-associated anemia is supported by the severe anemia seen in anephric patients.6 However, the mechanisms impairing renal EPO production are not well understood. The production capacity of EPO remains significant even in end stage renal disease (ESRD) as these patients have been shown to respond with increased EPO synthesis in the setting of an additional hypoxic stimulus.7 This suggests that the decrease in EPO production in CKD is, in part, a physiologic response to achieve a chronically reduced Hb concentration.

Typically, EPO is produced in the peritubular capillary endothelial cells in the kidney relying on a feed-back mechanism measuring total oxygen carrying capacity. Hypoxia inducible factor (HIF), which is produced in the kidney and other tissues, is a substance
whose spontaneous degradation is inhibited in the presence of decreased oxygen delivery due to anemia or hypoxemia. The continued presence of HIF leads to signal transduction and the synthesis of EPO. Therefore the usual response is increased EPO production in the setting of anemia. The EPO then binds to receptors on erythroid progenitor cells in the bone marrow, specifically the burst-forming units (BFU-E) and colony-forming units (CFU-E). With EPO present, these erythroid progenitors differentiate into reticulocytes and red blood cells (RBCs). The absence of EPO leads to programmed apoptosis. This is mediated by the Fas antigen. The decreased red blood cell production and continued loss of blood (by programmed red blood cell death) leads to worsening anemia.

There are other factors in chronic kidney disease which contribute to anemia. Acute and chronic inflammatory conditions have a significant impact on anemia in the CKD population by pro-inflammatory cytokines decreasing EPO production and inducing apoptosis in colony-forming unit-erythroid cells (CFU-E). The early induction of apoptosis in CFU-E cells stops the process of development into RBC. Inflammatory cytokines have also been found to induce the production of hepcidin, a recently discovered peptide generated in the liver, which interferes with RBC production by decreasing iron availability for incorporation into erythroblasts. This also impairs the production of RBC. Fig. 1 illustrates the above-mentioned interactions.

Red blood cells also have a decreased life span in patients with CKD. While the normal life span of an RBC is about 120 days, it has been demonstrated that this is shortened to only 60–90 days in CKD patients. In patients without CKD, the bone marrow has significant capacity to increase red blood cell production and to correct for the shortened life span, but this response is blunted in patients with CKD by the relative EPO deficiency. Uremic toxins have been implicated as contributing to apoptosis as the anemia will often improve after initiation of dialysis. There have been a number of prospective and observational studies that have demonstrated improved Hb levels and decreased dose of erythropoiesis-stimulating agents (ESAs) with increased adequacy of dialysis. It has been hypothesized that it is the middle molecules (molecular weight range of 500–2000 daltons) of uremia that contribute to bone marrow suppression.12

**Evaluation of anemia in patients with CKD**

As noted above, the prevalence of anemia in chronic kidney disease is as high as 10% in patients with CKD as early as stages 1 and 2. Since the consequences of untreated anemia can be severe, regular monitoring of the Hb level is needed for optimal care of this population. The 2006 National Kidney Foundation (NKF) Kidney Disease Outcomes Quality Initiative (KDOQI) clinical practice guidelines and clinical practice recommendations for anemia in CKD advocate annual screening for anemia of all patients with CKD. Further evaluation should be undertaken if anemia is present (Hb less than 13.5 g/dL in men and 12.0 g/dL in women per KDOQI guidelines). Note that the Hb thresholds for evaluation in the KDOQI guidelines do not separate menstruating versus non-menstruating women as the WHO guidelines do. This needs to be taken into consideration when evaluating women with early stages of CKD. These recommendations are also based on the assumption that these patients had normal blood counts in the past. A previous diagnosis of anemia secondary to other causes, such as thalassemias and sickle cell disease, may alter the decision tree for when and how to evaluate a patient's anemia. For example, a patient with sickle cell disease whose baseline Hb is about 8 g/dL when not in crisis, prior to any known renal disease, would be assessed differently from another patient without previous anemia who presents with CKD stage 3 and Hb of 10 g/dL.

The initial evaluation, when considering anemia related to CKD, is geared toward eliminating causes other than EPO deficiency. This is because EPO deficiency is a diagnosis of exclusion. As with any clinical evaluation, a thorough patient history is paramount. The history should include any prior diagnosis of anemia and the presence of symptoms related to anemia, such as fatigue, exercise

**Fig. 1. Erythropoiesis in chronic kidney disease.** Ag, antigen; EPO, erythropoietin; Fe, iron; IFN, interferon; IL, interleukin; RBCs, red blood cells; TNF, tumor necrosis factor. Courtesy of Iain Macdougall, MD. Reprinted with permission from National Kidney Foundation: Primer on Kidney Diseases, 5th Edition. Philadelphia: Saunders Elsevier 2009; 507.
intolerance, dyspnea, and changes in mentation. The laboratory evaluation should include a complete blood count with red blood cell indices, reticulocyte count, transferrin saturation (TSAT), and serum ferritin. A reticulocyte hemoglobin content (CHr), if available, may also be helpful in the diagnosis of iron deficiency. Typically the anemia of EPO deficiency is normocytic (normal mean corpuscular volume, or MCV) and normochromic (normal mean corpuscular hemoglobin concentration or MCHC). These can also be assessed when evaluating a peripheral smear. Macrocytosis (or low MCV) is suggestive of iron deficiency, but may also be seen in hemoglobinopathies such as thalassemia. Macrocytosis (or high MCV) could be suggestive of vitamin B12 or folate deficiency. If the MCV is high, or it is normal with a pleomorphic RBC smear or high red blood cell distribution width (RDW), folate and vitamin B12 levels should be checked.

In a steady state, serum ferritin levels correlate with the iron bound to tissue ferritin in the reticuloendothelial system. Serum ferritin does not carry or bind to iron. Its function is unknown, but is presumed to limit free iron, which is toxic to cells.14 Serum ferritin is also an acute phase reactant; therefore it increases in the setting of acute and chronic inflammation, independent of tissue iron stores. It is proposed that the elevated serum ferritin of inflammation decreases available iron and this limits the growth of pathogens that are iron dependent, such as bacteria and fungi.15 The TSAT is a measure of circulating iron which is available for delivery to the bone marrow. It is calculated by dividing the serum iron concentration by the total iron-binding capacity (TIBC) and then multiplying by 100. TIBC measures the maximum amount of iron the blood can carry, which indirectly measures transferrin since it is the most dynamic iron carrier. TIBC is used because it is less expensive than a direct measurement of transferrin. A TSAT of less than 16% in an anemic patient with CKD is consistent with a functional or an absolute iron deficiency. The normal levels for ferritin are 30–300 ng/mL in men and 15–250 ng/mL in women. Ferritin levels below these ranges are consistent with low total body iron stores and, along with a low TSAT, are diagnostic of absolute iron deficiency. Functional iron deficiency is seen when the ferritin levels are within or higher than the above-mentioned ranges and coincide with a low TSAT. This scenario is often observed with the administration of ESAs, which cause iron demand by the erythroid marrow to outstrip the ability of the reticuloendothelial system to release iron to circulating transferrin. Supply and demand are the problems in this state, not a total body iron deficiency.16

The hallmark of functional iron deficiency is that it responds to iron supplements with an increase in hemoglobin and/or decrease in ESA requirements. This is despite the normal or elevated ferritin levels. Patients with normal to elevated serum ferritin levels and low TSAT may not respond to intraavenous iron therapy, presumably due to reticuloendothelial blockade. This suggests that hepcidin has completely prevented the release of iron from macrophages to circulating transferrin. Hepcidin is an acute phase reactant protein produced in the liver. It inhibits intestinal iron absorption along with iron release from stores. In an inflammatory state the lower availability of iron has an antimicrobial effect.17 Since many microorganisms require iron to reproduce, the increased level of hepcidin, and the resulting decreased available iron, limits reproduction. Zaritsky et al. monitored hepcidin levels in patients with chronic kidney disease and performed a multivariate analysis comparing these levels with other indicators of anemia. Their findings suggest that increased hepcidin levels may contribute to abnormal iron regulation and erythropoiesis.18 There is no uniform testing or recommendations for testing, but this may be important for future evaluation of anemia.20

The reticulocyte count is an inexpensive and useful test in the evaluation of anemia. Reticulocytes are released into the circulation about two days prior to maturation into red blood cells. The reticulocyte count assesses the number and percentage of reticulocytes in circulating in the blood. Normally, about 1–2% of red blood cells in the circulation are reticulocytes. When the bone marrow is stimulated due to anemia, more reticulocytes are released into the blood, increasing their number and percentage. The reticulocyte count helps distinguish red blood cell underproduction from anemia caused by red blood cell loss or destruction. Since the typical reticulocyte count is represented as a percentage of total circulating red blood cells, a corrected reticulocyte count (or reticulocyte index) needs to be calculated to address the effect of anemia on the count. In anemia the reticulocyte percentage may be elevated, but the absolute number of reticulocytes is low. With inadequate or deficient EPO production in patients with CKD, the reticulocyte count would be expected to be low (absolute reticulocyte count

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**Fig. 2.** Flowchart for the evaluation of the chronic kidney disease patient with anemia. CBC, complete blood count; TIBC, total iron-binding capacity; Fe, iron; TSAT, transferrin saturation. Adapted from Kidney Disease Outcomes Quality Initiative: Am J Kidney Dis 2006;47(Suppl. 3):S1–145.
Anemia has a profound impact on patients with CKD. The most common symptoms are fatigue (both with activity and at rest), loss of libido, dizziness, shortness of breath, and decreased sense of well-being. These symptoms generally occur when the Hb is less than 10 g/dL and become more severe as Hb levels decrease further. Other more dangerous adverse outcomes include cardiovascular disease with left ventricular hypertrophy (LVH) and congestive heart failure. These may occur when the patient is otherwise asymptomatic and contribute to the excess cardiovascular morbidity and mortality rate observed among patients with CKD. In patients who already have coronary artery disease, decreased myocardial oxygen delivery may lead to worsening anginal symptoms. Decreased peripheral oxygen delivery due to anemia also leads to peripheral vasodilation, increased sympathetic nervous system activity, increased heart rate and stroke volume and, ultimately, LVH. It has been demonstrated that LVH strongly correlates with adverse outcomes (hospitalization and mortality) in patients with CKD. A 0.5 g/dL decrease in hemoglobin below normal correlates with a 32% increase in LVH risk, whereas a 5 mmHg increase in systolic blood pressure correlates with only an 11% increase in LVH risk.21

Anemia has also been associated with a decline in renal function in some patient groups. Decreased tissue oxygen delivery caused by anemia stimulates the renin-angiotensin-aldosterone system and contributes to renal vasoconstriction. These factors can further exacerbate proteinuria, which may lead to worsening renal failure. In patients with type 2 diabetes, anemia has been shown to be an independent risk factor to the progression of renal disease. Other complications associated with anemia consist of reduced cognitive function and mental acuity, impaired quality of life and the need for blood transfusion.24–27 Treatment of anemia associated with CKD has been shown to result in improved exercise capacity, energy, and physical mobility.25 Subjective symptoms also improve; such as quality of life, depression and cognition.26 Evidence supporting regression of LVH, fewer cardiac events or decreased mortality from ESA treatment is not compelling and will be discussed in greater detail below.

**Erythropoiesis-stimulating agents**

Since the introduction of recombinant human erythropoietin in the late 1980s, ESAs have become the mainstay of treatment of anemia in patients with CKD. Treatment with ESAs corrects the underlying pathophysiology of anemia in CKD while reducing the need for transfusions and their associated complications.28 The first ESA available was epoetin alfa and it was the only therapeutic option for over 10 years. Darbepoetin alfa became available in 2001. While both are approved by the US Food and Drug Administration (FDA) for the treatment of anemia in CKD and in cancer patients,29–32 only epoetin alfa is also FDA approved for the treatment of anemia associated with HIV and prior to major surgeries with the risk for increased blood loss.30,31 Epoetin alfa has a shorter half-life than darbepoetin alfa, although the half-life of both drugs is extended when they are administered subcutaneously. Although the bioavailability of subcutaneous epoetin alfa is between 20% and 30%, the prolonged half-life following subcutaneous injection, compared with IV infusion, potentially allows less frequent injections. The dose of epoetin alfa required to achieve the same hemoglobin response is about 30% lower with subcutaneous compared with intravenous administration.33 Darbepoetin alfa does not show any significant difference in Hb dose response between the subcutaneous and intravenous routes of administration. The package inserts suggest using epoetin alfa three times a week and darbepoetin alfa once a week, although darbepoetin has also been approved by the FDA for use every two weeks.29–31 Both ESAs have been shown to have success with extended dosing intervals. A retrospective review of the extended dosing of epoetin alfa with intervals ranging from weekly to biweekly to once every three weeks was reported by Germain et al., with the most common dosing interval every two weeks.24 In this study, hemoglobins were maintained at greater than 11 g/dL in 82% of patients. The PROMPT study was a randomized prospective trial in which patients were administered epoetin alfa at intervals of every one, two, three or four weeks.35 Hemoglobin levels were maintained above 11 g/dL in 90% of patients on every two-week dosing intervals and 75% in groups with every three-week and every four-week dosing intervals. Similar studies have been performed with darbepoetin alfa. Jadoul et al. examined hemodialysis patients on every two-week dosing and when extended to every four-week dosing, 83% of the patients maintained hemoglobin levels above target.36 This was a small study, but a later, larger study confirmed the efficacy of the extended dosing in CKD patients.37

There are ESAs that are currently in use in countries other than the United States. Epoetin beta is similar to epoetin alfa in its efficacy, safety, pharmacokinetics and pharmacodynamics. Continuous erythropoietin receptor activator (CERA) was created by integrating a large polymer chain into the erythropoietin molecule. It has been shown to have an extended half-life of about 130 h which is independent of intravenous or subcutaneous administration. There are other treatments for the anemia of CKD currently in clinical development. Hematide is an erythropoietin-mimetic peptide, the amino acid sequence of which is completely unrelated to native or recombinant erythropoietin but shares the same functional and biologic properties.38 Hypoxia inducible factor
symptoms associated with anemia. ESAs also reduce the need for transfusions, thereby decreasing the risks of immunologic sensitization, infections and iron overload. Although a survival advantage among CKD patients treated with ESAs has not been demonstrated in randomized clinical trials, a two-year historical cohort study showed that those hemodialysis patients treated with ESAs lived longer than those not treated. Observational studies have suggested increased survival among hemodialysis patients with Hb levels greater than 12 g/dL. But randomized control trials with higher target hemoglobins have not shown a reduction of death or cardiovascular events. The largest of these trials in hemodialysis patients demonstrated higher mortality rates in patients with targeted hemoglobin greater than 14 than those patients with targeted hemoglobins of 10.

There is debate about the effect of ESAs on the progression of renal failure. Roth et al. conducted a 48-week randomized open-label trial comparing patients with chronic kidney disease who received epoetin alfa versus those who did not receive any ESA. CKD was defined by serum creatinine of $3–8 \text{ mg/dL}$ and serial GFRs were measured using $^{125}\text{I}-\text{iothalamate}$ clearance. The target hematocrit was 35% (equal to hemoglobin of 11.7 g/dL) for those patients receiving epoetin alfa. The study demonstrated no difference in the mean change of glomerular filtration rate from initial to the last available calculation. The study was not powered to assess if different starting GFRs made a difference in the outcome. A randomized controlled trial by Gouva et al. showed treatment with epoetin alfa to a target hemoglobin of greater than 13 g/dL in patients with chronic kidney disease slowed the progression of renal disease. The need for renal replacement therapy was actually reduced by 60%. More recent data suggest that any benefit on the progression of renal disease from ESA therapy depends on the hemoglobin target. Higher hemoglobin targets have been shown to increase the rate of initiation of dialysis.

Renal anemia causes increased sympathetic nerve activity and is linked to cardiovascular complications, such as increased blood pressure and left ventricular hypertrophy. Treatment with ESAs improves heart failure symptoms and leads to regression of left ventricular hypertrophy. This is seen with lower hemoglobin targets (10–11 g/dL). Risks associated with higher hemoglobin targets (greater than 13 g/dL) will be discussed later in this article.

Several studies have suggested that the administration of ESAs to anemic CKD patients decreases hospitalizations and thereby reduces the overall cost of care. Furthermore, there are data to suggest that ESA-treated anemic CKD patients are more productive workers and consume fewer resources.

Despite the numerous physiologic benefits of ESA therapy among patients with CKD, there are risks. Randomized controlled trials have shown increased rates of cardiovascular complications in hemodialysis patients with high (13–15 g/dL) versus low (10–11.5 g/dL) hemoglobin targets. The Cardiovascular Risk Reduction of Early Anemia Treatment with Epoetin Beta (CREATE) trial is a prominent randomized clinical trial addressing Hb targets. In this study 603 patients were enrolled from 94 centers in 22 countries and were randomly assigned to two treatment groups to test the hypothesis that complete correction of anemia in patients with stages three to four CKD improves cardiovascular outcomes as compared with partial correction of anemia. The eligible patients were over 18 years of age with mild to moderate chronic anemia related to their chronic kidney disease, a glomerulatation rate of 15.0–35.0 mL/min (by the Cockcroft–Gault formula) and a blood pressure less than 170/95. Patients with advanced cardiovascular disease, non-renal cause of anemia, previous ESA treatment, and anticipated need for renal replacement therapy within six months were excluded. This was an open-label, randomized two-group study with parallel group design. Patients with moderate anemia (Hb, 11.0–12.5 g/dL) were randomized to receive either early or late treatment with epoetin beta, an ESA primarily used overseas, especially in Europe. The immediate treatment group had a hemoglobin goal of 13–15 g/dL and the delayed treatment group had a lower target of 10.5–11.5 g/dL. For the second group, treatment was delayed until the hemoglobin dropped below 10.5 g/dL. This trial’s primary endpoint was a composite of eight cardiovascular events. Secondary endpoints included left ventricular mass index, quality of life scores, and the progression of chronic kidney disease. There was no statistically significant difference in the risk of cardiovascular events between the two groups (58 versus 47 in high and low groups retrospectively, hazard ratio of 0.78, 95% confidence interval 0.53–1.14, with a P value of 0.20), although the trend was toward increased events in high-target hemoglobin group. Left ventricular hypertrophy remained stable in both groups. Quality of life was the only endpoint that was significantly better in the high-target treatment arm. All other events were not statistically significant in their differences.

The Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) trial was an open-label, prospective, randomized trial comparing the effect of correcting hemoglobin to a target of 13.5 g/dL versus a target of 11.3 g/dL. This trial enrolled 1432 patients at 130 sites within the US, over 18 years of age, who had hemoglobin less than 11.0 g/dL and CKD defined by an estimated glomerular filtration rate of 15–50 mL/min by Modification of Diet in Renal Disease (MDRD) formula. Patients were excluded if they had uncontrolled hypertension, active gastrointestinal bleeding, iron overload, frequent transfusions in the previous six months, active cancer, angina, or previous treatment with epoetin alfa. Two randomly assigned groups of patients received epoetin alfa. Group 1 had a target hemoglobin of 13–13.5 g/dL, which was later amended to 13.5 g/dL. Group 2 had a target hemoglobin of 10.5–11.0 g/dL, which was later changed to 11.3 g/dL. Epoetin alfa was initially administered weekly, but was allowed to be decreased every other week if the hemoglobin level was stable. The patients in the higher hemoglobin group had a significantly higher incidence of the composite end-point (death, myocardial infarction, hospitalization for congestive heart failure and stroke), congestive heart failure, death, and hospitalization (cardiovascular and all-cause). There was no difference between the groups in the rate of stroke, myocardial infarction, or renal replacement therapy or in quality of life.

Treatment with ESAs has been reported to increase the risk of adverse events in other studies. Patients with congestive heart failure or ischemic heart disease treated with ESAs had an increased risk of mortality and of non-fatal MI, vascular access thrombosis, and other thrombotic events when epoetin alfa was dosed to target hematocrit of 42%. Following the publication of such studies, including CHOIR and CREATE, along with the studies on cancer patients with higher targeted hemoglobin and worse outcomes, the FDA issued a “black box” warning. The warning advises physicians that patients experienced greater risks for death and serious cardiovascular events when administered ESAs to target higher versus lower Hb levels (12.5 versus 11.3 g/dL; 14 versus 10 g/dL). The FDA recommends individualized dosing to achieve and maintain Hb levels within the range of 10–12 g/dL. This FDA recommendation is at odds with the US National Kidney Foundation’s Kidney Disease Outcomes Quality Initiative (NKF/KDOQI) anemia guidelines which recommend a target Hb of 11–12 g/dL, not to exceed 13 g/dL in anemic CKD patients treated.
with ESAs. The bottom line is that the target Hb level should be individualized to the patient's symptoms, co-morbidities, and ESA responsiveness within the range specified by the FDA, NKF/KDOQI or other national evidenced based guideline.

In its own retrospective analysis of the normal hematocrit trial in hemodialysis patients and the CHOIR study of CKD patients the FDA noted that the rate of rise of Hb in ESA-treated patients was an independent risk factor for adverse outcomes irrespective of the ESA dose and target Hb level. As a result, the FDA cautions against a Hb rise of >2 g/dL in a four-week period and recommends a 25% ESA dose reduction in such patients. The FDA also recommends a 25% ESA dose reduction in patients trending toward exceeding the Hb target range ceiling of 12 g/dL.

Although the intention to treat analysis of the CHOIR study indicates a higher risk for the composite outcomes of death and cardiovascular events among patients randomized to the higher Hb target, a secondary analysis of the CHOIR study by Sczcech et al. reveals that when the analysis is adjusted for ESA dose and patients not achieving their Hb target, the difference in outcomes between the high and low Hb targets becomes non-significant and the use of a high dose of ESA becomes the major predictor of adverse outcomes in both target groups. The analysis cannot distinguish whether this effect is due to toxicity of high doses of ESA per se and/or whether patient factors resulting in ESA resistance (e.g. inflammation) account for the higher incidence of adverse events. Nonetheless, it seems prudent to avoid high doses of ESAs (defined as >20,000 units/week epoetin alfa in the CHOIR study) in ESA-resistant patients. Occasional excursions of Hb to the 12–13 g/dL range is usually sufficient in patients with CKD not yet on dialysis or peritoneal dialysis patients when taking ESAs. The target Hb level is greater than 20%. While this is the recommended target, the lowest all-cause and cardiovascular death risks where observed in patients with TSATs in the 30–50% range.

Another reported adverse effect of ESA therapy is hypertension. It is caused by multiple mechanisms including: expansion of blood volume, reversal of hypoxic vasodilation and increased blood viscosity. A direct vasoconstrictive effect has also been proposed. The hypertension related to treatment is more common in patients receiving hemodialysis, associated with a rapid rise in Hb level and usually is seen within the first 90 days of treatment. Rarely, seizures and hypertensive encephalopathy have occurred. Antihypertensive treatment may need to be adjusted, so close monitoring of the patient's blood pressure is recommended.

A rare and serious complication associated with ESAs is pure red cell aplasia (PRCA). PRCA is a result of the production of anti-erythropoietin antibodies induced by the administration of exogenous ESAs. This was primarily associated with the subcutaneous use of epoetin beta sold outside of the United States. It was thought to be secondary to the additive Tween 80 used to stabilize the substance. Tween 80 was never used in the United States and PRCA remains rare in the US. PRCA should be suspected if a patient has a sudden weekly drop in hemoglobin of about 1 g/dL or a weekly transfusion requirement and a low reticulocyte count, despite a high dose of an ESA for several months. White blood cell and platelet counts remain unaffected, differentiating this condition from aplastic anemia. Iron deficiency also should be considered; this will be discussed later in the article. PRCA is definitively diagnosed when anti-erythropoietin antibodies are demonstrated in the blood, or an examination of the bone marrow reveals normal cellularity and less than 4% erythroblasts. PRCA is treated by discontinuing the ESA and administering immunosuppressive therapy. Patients generally respond after several months of treatment and usually do not relapse after immunosuppressants are discontinued.

Iron therapy

Many anemic patients with CKD and inadequate EPO production have coexisting iron deficiency. Iron deficiency almost always is present in hemodialysis patients due to: bleeding when needles are removed from the vascular access, blood infiltration of the vascular access, vascular access procedures, frequent blood testing, and clotting or general blood loss in the extracorporeal circuit. The iron deficiency observed in patients with CKD not yet on hemodialysis, and those on peritoneal dialysis, is often due to decreased oral iron intake from the prescribed dietary protein restriction or decreased appetite for red meat. Iron deficiency often develops, if it is not present initially, while a patient is receiving ESA therapy. This is due to depletion of the existing iron stores with the stimulation of new RBC production. Regular monitoring of iron status is essential during the initiation of ESA therapy with monthly assessment of serum ferritin and TSAT while the Hb level is rising and then every three months after the Hb level has stabilized. The target levels for serum ferritin and TSAT are higher in ESA-treated patients than in the general population because of the development of functional iron deficiency, in which the demand for iron by the ESA-stimulated bone marrow exceeds the rate at which normal reticuloendothelial iron stores can release it. The NKF/KDOQI anemia guidelines recommend a target serum ferritin of greater than 200 ng/mL in hemodialysis patients and greater than 100 ng/mL in patients with CKD not receiving hemodialysis and those receiving peritoneal dialysis patients when taking ESAs. The target TSAT level is greater than 20%. While this is the recommended target, the lowest all-cause and cardiovascular death risks where observed in patients with TSATs in the 30–50% range.

Iron can be administered orally or intravenously. Oral iron is usually sufficient in patients with CKD not yet on dialysis or peritoneal patients who do not have the continual blood loss that is typical in hemodialysis patients. Yet even in non-hemodialysis patients, oral iron may not be effective due to gastrointestinal side effects, poor compliance or the severity of iron deficiency. Oral iron salts such as ferrous sulfate, gluconate and fumarate should be administered one hour before or 2 h after meals to result in the greatest absorption. Oral ferrous iron salts must be oxidized to the ferric form by stomach acid to allow absorption by the small intestine. This step can be impaired by food, antacids, histamine-2 blockers or proton pump inhibitors. It has been shown that the minimal effective dose is 200 mg of elemental iron daily. Each 325 mg tablet of ferrous sulfate contains 65 mg of elemental iron; therefore three tablets must be administered over the course of each day. As a result of inflammation or impaired iron mobilization from stores, serum ferritin is often elevated in patients with chronic kidney disease. This further reduces bioavailability of oral iron to only 1–2%, so even the most compliant patients may not be able to replete their iron stores with oral iron.

In CKD patients with mild to moderate iron deficiency, a three-month trial of oral iron is recommended to assess the effectiveness of that route of administration. For patients with severe iron deficiency and all iron deficient hemodialysis patients, intravenous iron supplements are recommended. There are four preparations of intravenous iron currently available in the US: iron dextran, iron sucrose, iron gluconate and ferumoxytol. The least expensive, and the one approved by the FDA to be given in doses as large as 1000 mg, is iron dextran, but it has been associated with fatal anaphylactic reactions. As a result, FDA has issued a “black box” warning recommending that patients undergo a 25 mg test dose the first time the drug is given. If a patient does not have an adverse reaction to this dose, he/she is less likely to have an anaphylactic reaction to the therapeutic dose of iron dextran, but fatal anaphylactic reactions still occur with an uneventful test dose. This risk notwithstanding, the use of a single iron dextran dose of 500–1000 mg is appealing in non-hemodialysis patients who need to travel long distances in order to receive their treatment. Furthermore, fewer IV iron doses also means fewer intravenous line placements and therefore the preservation of the veins needed for the
creation of permanent dialysis access for future hemodialysis. Iron sucrose and iron gluconate do not require a test dose because they have not been associated with fatal anaphylactic reactions. These two preparations are FDA approved to be given in doses up to 250–300 mg, meaning non-hemodialysis patients will need more trips to the clinic or hospital for infusions and more placements of intravenous catheters to receive a total repletion dose of 1000 mg. These preparations have some non-fatal adverse reactions such as nausea, vomiting, and hypotension. Generally, with slower infusions of these medications, there is a decreased risk of adverse side effects. Ferumoxytol, which was approved by the FDA in June 2009, is an iron dextran nanoparticle which can be administered in rapid injection of up to 510 mg over 17 s. In phase 3 studies in non-dialysis patients with CKD and iron deficiency anemia, it was shown to have no more side effects than oral iron and to be more effective in raising the Hb level than an ESA with oral iron.62

Despite the benefits of iron supplementation, concerns have been raised about potential toxicity of intravenous iron including cellular and vascular damage resulting from oxidative stress and impaired white blood cell function based on in vitro studies. In patients with CKD receiving intravenous iron sucrose, there has been evidence of increased urinary excretion of markers of tubular injury, but no increase in albuminuria. This has not proved to be clinically significant in other studies. There was no increase in hospitalizations or mortality seen in observational studies in hemodialysis patients receiving less than 400 mg on average of intravenous iron per month.60,63,64 Intravenous iron was not shown to be a risk factor for bacteremia in hemodialysis patients in a multivariate analysis.65 Serial liver biopsies were done in patients with hemochromatosis and showed no significant organ injury when serum ferritin level was less than 2000 ng/ml.66 The NKF/KDOQI anemia guidelines recommend weighing ESA responsiveness, hemoglobin concentration, TSAT level, and the patient's clinical status when considering giving iron to a patient with a ferritin greater than 500 ng/mL.

ESA resistance

ESA resistance is defined as a failure to achieve a target hemoglobin greater than 11.0 g/dL in the setting of an epoetin alfa dose of more than 500 units/kg per week or the equivalent of another ESA. The causes can include iron deficiency, acute and chronic inflammatory conditions, severe hyperparathyroidism, aluminum toxicity, folate deficiency and PRCA. Iron deficiency is the most common cause of ESA resistance, but it is followed closely by inflammation and infection. The source of inflammation or infection may be difficult to elucidate, but it is often associated with high levels of acute phase reactants, such as ferritin, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP). The use of dialysis catheters for vascular access has been shown to lower Hb levels and increase ESA requirements. This may reflect an inflammatory state induced by the presence of a catheter and its biofilm without evidence of an active infection demonstrated by positive cultures.67

The resistance to ESA therapy in the inflammatory state has led to exploration of adjuvant treatment with vitamin C. Studies have not shown significant benefit in patients with CKD not yet on dialysis treated with vitamin C, although there have been many smaller studies showing decreased ESA requirements with concomitant use of vitamin C in patients undergoing hemodialysis.68–72 Vitamin C therapy may produce some benefit in patients with CKD or undergoing peritoneal dialysis receiving oral iron, as it may promote intestinal iron absorption. There have been several studies examining the use of L-carnitine as an adjuvant therapy for anemia, but the evidence has been lacking its efficacy in patients with non-dialysis CKD. There has been some benefit in reducing ESA doses in a subgroup of hemodialysis patients, but it is not recommended for all patients.74,75 Prior to the advent of ESA therapy, androgens were used with some success in treating anemia in hemodialysis patients, but with significant side effects. However evidence is lacking for any benefit of androgen use in patients receiving adequate ESA therapy and long-term androgen use has the potential for significant toxicity.

Even with sufficient dosing of ESAs and iron therapy, patients may still require red blood cell transfusions due to ESA resistance or acute blood loss. In patients who are candidates for organ transplantation, this is the option of last resort because sensitization from transfusion can decrease the chance of a successful transplant. There also still exists the small risk of bloodborne infections such as hepatitis and human immunodeficiency virus. Unlike the guidelines for ESA therapy, there is no recommended Hb threshold at which a patient should be transfused. This is a clinical decision based primarily on a patient’s symptoms, but must also take into consideration acuity of Hb decline, concomitant diseases such as coronary artery disease, and the patient’s candidacy for future organ transplantation.

Conclusions

Anemia is a common and important complication among patients with CKD and health care professionals should be familiar with the best practices for its screening, evaluation and treatment. Untreated anemia places patients at risk for cardiovascular events, more rapid progression of chronic kidney disease and significantly decreased quality of life. The cause of anemia is multifactorial in patients with CKD, but inadequate production of EPO by the diseased kidneys is the common denominator. The anemia generally becomes more severe as a patient’s renal function declines. Once other treatable causes of anemia are evaluated and addressed, patients who remain anemic will likely need to be treated with an ESA. According to the NKF/KDOQI guidelines, ESA therapy should be initiated when the patient’s Hb drops below 10 g/dL, with target Hb level for treatment being 11–12 g/dL. It is also recommended not to treat patients with ESAs to Hb above 13 g/dL as studies have shown evidence of adverse events in patients with CKD maintained at normal Hb levels without significant benefit. Both prior to and during ESA treatment, patients with CKD often require iron supplementation. This is frequently given orally in patients with CKD not on hemodialysis and in patients on peritoneal dialysis. Hemodialysis patients and those unable to respond oral iron require intravenous iron therapy. Intravenous iron therapy is associated with adverse effects, including potentially fatal anaphylactic reactions to iron dextran, but it also has significant benefits by increasing Hb levels and decreasing ESA requirements. Despite adequate treatment with iron and ESAs, patients may fail to increase Hb and require transfusion. As more is learned about anemia in patients with CKD, treatment methods and goals may continue to evolve, but there is no question that current treatments have significantly improved the quality of life and decreased transfusions and their complications in this vulnerable population.

Practice points

- Anemia is a common complication in patients with chronic kidney disease (CKD) and is associated with adverse outcomes including poor quality of life, cardiovascular disease and progression of renal failure.
- Evaluation of CKD patients with anemia is straightforward and is directed at ruling out iron deficiency and, if clinically
indicated, other etiologies such as hemoglobinopathies, blood loss and vitamin deficiencies.

- Most anemic patients with CKD will have erythropoietin deficiency, which is a diagnosis of exclusion.
- Treatment of anemia in patients with CKD includes erythropoiesis-stimulating agents (ESAs), but attention must be paid to repletion and maintenance of iron stores.
- The target hemoglobin level for anemic CKD patients receiving ESA therapy is 10–12 g/dL per the US Food and Drug Administration.
- Maintenance of hemoglobin levels above 13 g/dL with ESA therapy has been associated with and increased frequency of adverse cardiovascular events in randomized clinical trials.
- When used according to practice guidelines, ESA therapy has been associated with improved quality of life, reduction in transfusion requirements and few significant adverse effects.

**Conflicts of interest**

CL reports no conflicts of interest. JW has served on advisory boards for Amgen, Centocor Ortho Biotech, Watson, Affymax and AMAG, in addition to serving on speakers bureaus for Amgen, Watson, and AMAG.

**References**


