CME CREDIT *EDUCATIONAL OBJECTIVE:* Readers will anticipate anemia in patients with chronic kidney disease and will treat it conservatively

GEORGES NAKHOUL, MD
Department of Nephrology and Hypertension, Glickman Urological and Kidney institute, Cleveland Clinic

JAMES F. SIMON, MD
Department of Nephrology and Hypertension, Glickman Urological and Kidney institute, Cleveland Clinic; Assistant Professor, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH

Anemia of chronic kidney disease: Treat it, but not too aggressively

ABSTRACT

Anemia of renal disease is common and is associated with significant morbidity and death. It is mainly caused by a decrease in erythropoietin production in the kidneys and can be partially corrected with erythropoiesis-stimulating agents (ESAs). However, randomized controlled trials have shown that using ESAs to target normal hemoglobin levels can be harmful, and have called into question any benefits of ESA treatment other than avoidance of transfusions.

KEY POINTS

Before treating with ESAs, it is necessary to investigate and rule out underlying treatable conditions such as iron or vitamin deficiencies.

Recognizing anemia in chronic kidney disease is important and often involves participation by the primary care physician, especially in early disease when chronic kidney disease may be mild.

The only proven benefit of ESA therapy is avoidance of blood transfusions.

ESAs should not be used to increase the hemoglobin concentration above 13 g/dL. In end-stage renal disease, the goal of therapy is to maintain levels at a target no higher than 11.5 g/dL. In nondialysis-dependent chronic kidney disease, the decision to prescribe ESA therapy should be individualized.

Dr. Simon has disclosed membership on advisory committee or review panels and teaching and speaking for Alexion, and consulting for Regulus.

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Anemia is a frequent complication of chronic kidney disease, occurring in over 90% of patients receiving renal replacement therapy. It is associated with significant morbidity and mortality. While its pathogenesis is typically multifactorial, the predominant cause is failure of the kidneys to produce enough endogenous erythropoietin. The clinical approval of recombinant human erythropoietin in 1989 dramatically changed the treatment of anemia of chronic kidney disease, but randomized controlled trials yielded disappointing results when erythropoiesis-stimulating agents (ESAs) were used to raise hemoglobin to normal levels.

This article reviews the epidemiology and pathophysiology of anemia of chronic kidney disease and discusses the complicated and conflicting evidence regarding its treatment.

DEFINITION AND PREVALENCE

Anemia is defined as a hemoglobin concentration less than 13.0 g/dL for men and less than 12.0 g/dL for premenopausal women.[1] It is more common in patients with impaired kidney function, especially when the glomerular filtration rate (GFR) falls below 60 mL/min. It is rare at GFRs higher than 80 mL/min,[2] but as the GFR falls, the severity of the anemia worsens[3] and its prevalence increases: almost 90% of patients with a GFR less than 30 mL/min are anemic.[4]

RENAL ANEMIA IS ASSOCIATED WITH BAD OUTCOMES

Anemia in chronic kidney disease is independently associated with risk of death. It is also an all-cause mortality multiplier, ie, it magnifies the risk of death from other disease states.[5]

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In observational studies, anemia was associated with faster progression of left ventricular hypertrophy, inflammation, and increased myocardial and peripheral oxygen demand, thereby leading to worse cardiac outcomes with increased risk of myocardial infarction, coronary revascularization, and readmission for heart failure.[6–8] Anemia is also associated with fatigue, depression, reduced exercise tolerance, stroke, and increased risk of rehospitalization.[9–13]

RENAL ANEMIA IS MULTIFACTORIAL

Anemia of chronic kidney disease is typically attributed to the decrease of erythropoietin production that accompanies the fall in GFR. However, the process is multifactorial, with several other contributing factors: absolute and functional iron deficiency, folate and vitamin B_{12} deficiencies, reduced red blood cell life span, and suppression of erythropoiesis by the uremic milieu.[14]

While it was once thought that chronic kidney disease leads to loss of erythropoietin-producing cells, it is now known that downregulation of hypoxia-inducible factor (HIF; a transcription factor) is at least partially responsible for the decrease in erythropoietin production[15,16] and that this downregulation is reversible (see below).

Almost 90% of patients with a GFR < 30 mL/min are anemic

ERYTHROPOIETIN, IRON, AND RED BLOOD CELLS

Erythropoietin production is triggered by hypoxia, mediated by HIF

Erythropoietin is produced primarily in the deep cortex and outer medulla of the kidneys by a special population of peritubular interstitial cells.[17] The parenchymal cells of the liver also produce erythropoietin, but much less.[18]

The rate of renal erythropoietin synthesis is determined by tissue oxygenation rather than by renal blood flow; production increases as the hemoglobin concentration drops and the arterial oxygen tension decreases (**Figure 1**).[19]

The gene for erythropoietin is located on chromosome 7 and is regulated by HIF. HIF molecules are composed of an alpha subunit, which is unstable at high Po_2, and a beta subunit, constitutively present in the nucleus.[20]

In hypoxic conditions, the HIF dimer is transcriptionally active and binds to specific DNA recognition sequences called *hypoxia-response elements*. Gene transcription is upregulated, leading to increased production of erythropoietin.[21]

Under normal oxygen tension, on the other hand, the proline residue of the HIF alpha subunit is hydroxylated. The hydroxylated HIF alpha subunit is then degraded by proteasomal ubiquitylation, which is mediated by the von Hippel-Lindau tumor-suppressor gene *pVHL*.[22] Degradation of HIF alpha prevents formation of the HIF heterodimers. HIF therefore cannot bind to the hypoxia-response elements, and erythropoietin gene transcription does not occur.[23]

Thus, in states of hypoxia, erythropoietin production is upregulated, whereas with normal oxygen tension, production is downregulated.

Erythropoietin is essential for terminal maturation of erythrocytes

Erythropoietin is essential for terminal maturation of erythrocytes.[24] It is thought to stimulate the growth of erythrogenic progenitors: burst-forming units-erythroid (BFU-E) and colony-forming units-erythroid (CFU-E). In the absence of erythropoietin, BFU-E and CFU-E fail to differentiate into mature erythrocytes.[25]

Binding of erythropoietin to its receptor sets off a series of downstream signals, the most important being the signal transducer and activator of transcription 5 (STAT5). In animal studies, STAT5 was found to inhibit apoptosis through the early induction of an antiapoptotic gene, *Bcl-xL*.[26]

Iron metabolism is controlled by several proteins

Iron is characterized by its capacity to accept or donate electrons. This unique property makes it a crucial element in many biochemical reactions such as enzymatic activity, DNA synthesis, oxygen transport, and cell respiration.

Iron metabolism is under the control of several proteins that play different roles in its absorption, recycling, and loss (**Figure 2**).[27]

Dietary iron exists primarily in its poorly soluble trivalent ferric form (Fe^{3+}), and it needs to be reduced to its soluble divalent fer-

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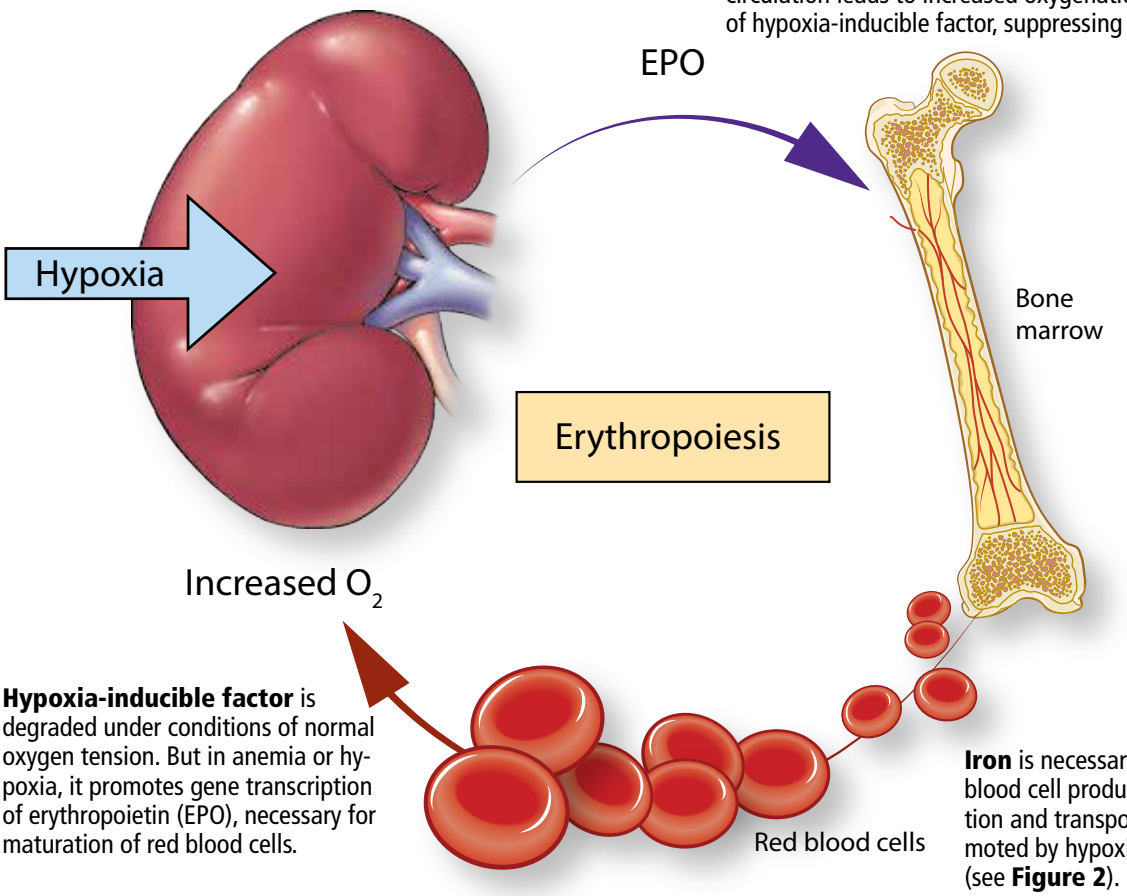
Erythropoiesis: A homeostatic system

Erythropoietin (EPO) promotes production of mature red blood cells in the bone marrow. More red blood cells in the circulation leads to increased oxygenation and lower levels of hypoxia-inducible factor, suppressing EPO production.



Hypoxia-inducible factor is degraded under conditions of normal oxygen tension. But in anemia or hypoxia, it promotes gene transcription of erythropoietin (EPO), necessary for maturation of red blood cells.

Iron is necessary as well for red blood cell production. Its absorption and transport are also promoted by hypoxia-inducible factor (see **Figure 2**).

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FIGURE 1.

rous form (Fe^{2+}) by ferric reductase to be absorbed. Ferrous iron is taken up at the apical side of enterocytes by a divalent metal transporter (DMT1) and is transported across the brush border.[28]

To enter the circulation, iron has to be transported across the basolateral membrane by a transporter called ferroportin.[29] Ferroportin is also found in placental syncitiotrophoblasts, where it transfers iron from mother to fetus, and in macrophages, where it allows recycling of iron scavenged from damaged cells back into the circulation.[30] Upon its release, the ferrous iron is oxidized to the ferric form and loaded onto transferrin. This oxidation process involves hephaestin, a homologue of the ferroxidase ceruloplasmin.[31]

In the plasma, iron is bound to transferrin, and under normal circumstances one-third of transferrin is saturated with iron.[32] Transferrin receptors are present on most cells but are most dense on erythroid precursors. Each transferrin receptor can bind two transferrin molecules. After binding to transferrin, the transferrin receptor is endocytosed, and the iron is released into acidified vacuoles. The transferrin-receptor complex is then recycled to the surface.[33]

Ferritin is the cellular storage protein for iron, and it can store up to 4,500 atoms of iron within its spherical cavity.[34] The serum level of ferritin reflects overall storage, with 1 ng/mL of ferritin indicating 10 mg of total iron stores.[35] Ferritin is also an acute-phase reactant, and plasma levels can increase in inflammatory states such as infection or malignancy. As such, elevated ferritin does not necessarily indicate elevated iron stores.

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Iron: From gut to hemoglobin

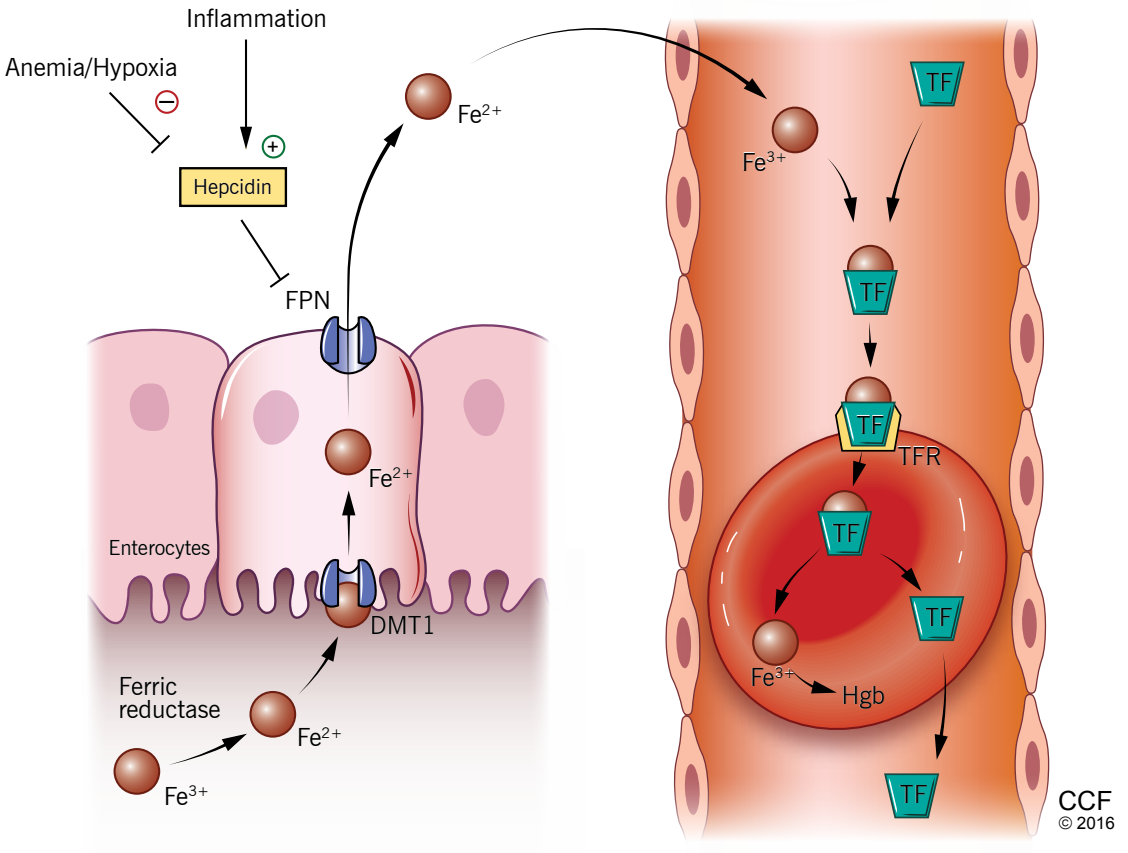

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FIGURE 2. Iron absorption and metabolism is controlled by several proteins.

DMT1 = divalent metal transporter 1; FPN = ferroportin; Hgb = hemoglobin; TF = transferrin, TFR = transferrin receptor

Hypoxia-inducible factor downregulation is partially responsible for the decrease in erythropoietin production

Iron is lost in sweat, shed skin cells, and sloughed intestinal mucosal cells. However, there is no specific mechanism of iron excretion from the human body. Thus, iron is mainly regulated at the level of intestinal absorption. The iron exporter ferroportin is upregulated by the amount of available iron and is degraded by hepcidin.[36]

Hepcidin is a small cysteine-rich cationic peptide that is primarily produced in the liver, with some minor production also occurring in the kidneys.[37] Transcription of the gene encoding hepcidin is downregulated by anemia and hypoxia and upregulated by inflammation and elevated iron levels.[38] Transcription of hepcidin leads to degradation of ferroportin and a decrease in intestinal iron absorption. On the other hand, anemia and hypoxia inhibit hepcidin transcription, which allows ferroportin to facilitate intestinal iron absorption.

TREATMENT OF RENAL ANEMIA

Early enthusiasm for erythropoietin agents

Androgens started to be used to treat anemia of end-stage renal disease in 1970,[39,40] and before the advent of recombinant human erythropoietin, they were a mainstay of nontransfusional therapy for anemic patients on dialysis.

The approval of recombinant human erythropoietin in 1989 drastically shifted the treatment of renal anemia. While the initial goal of treating anemia of chronic kidney disease with erythropoietin was to prevent blood transfusions,[41] subsequent studies showed that the benefits might be far greater. Indeed, an initial observational trial showed that erythropoiesis-stimulating agents (ESAs) were associated with improved quality of life,[42] improved neurocognitive function,[43,44] and even cost savings.[45] The benefits also extended

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TABLE 1

Four randomized controlled trials of hemoglobin-raising in chronic kidney disease

	NHCT[52]	CHOIR[53]	CREATE[54]	TREAT[55]
Population	Patients with chronic heart failure and end-stage renal disease on dialysis	Chronic kidney disease	Chronic kidney disease	Chronic kidney disease with diabetes
Hemoglobin target	10 vs 14 g/dL	13.5 vs 11.3 g/dL	> 13 vs 11 g/dL	> 13 vs 9 g/dL
Target achieved?	No	No	Yes	No
Primary outcomes	Time to death or first myocardial infarction	Composite of death, myocardial infarction, hospitalization for chronic heart failure, stroke	Time to first cardiovascular event	Composite of death or a cardiovascular event and death or end-stage renal disease
Risks with higher hemoglobin level	Trend toward increased risk of primary outcome resulted in early study interruption	Increased risk of primary outcome	Trend toward risk increase that was nonsignificant: no benefits	No risk increase or reduction
Other results	Higher rate of thrombosis in high-target group		Improved quality of life	Higher rate of stroke

NHCT = Normal Hematocrit Study,[52] CHOIR = Correction of Hemoglobin and Outcomes in Renal Insufficiency trial,[53] CREATE = Cardiovascular Risk Reduction by Early Anemia Treatment trial,[54] TREAT = Trial to Reduce Cardiovascular Events With Aranesp Therapy[55]

Erythropoietin production is upregulated in hypoxia but downregulated in normal oxygen tension

to major outcomes such as regression of left ventricular hypertrophy,[46] improvement in New York Heart Association class and cardiac function,[47] fewer hospitalizations,[48] and even reduction of cardiovascular mortality rates.[49]

As a result, ESA use gained popularity, and by 2006 an estimated 90% of dialysis patients were receiving these agents.[50] The target and achieved hemoglobin levels also increased, with mean hemoglobin levels in hemodialysis patients being raised from 9.7 to 12 g/dL.[51]

Disappointing results in clinical trials of ESAs to normalize hemoglobin

To prospectively study the effects of normalized hemoglobin targets, four randomized controlled trials were conducted (**Table 1**):

- The Normal Hematocrit Study (NHCT)[52]
- The Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) trial[53]
- The Cardiovascular Risk Reduction by Early Anemia Treatment (CREATE) trial[54]
- The Trial to Reduce Cardiovascular Events With Aranesp Therapy (TREAT).[55]

These trials randomized patients to either higher "normal-range" hemoglobin targets or to lower target hemoglobin levels.

Their findings were disappointing and raised several red flags about excessive use of ESAs. The trials found no benefit in higher hemoglobin targets, and in fact, some of them demonstrated harm in patients randomized to higher targets. Notably, higher hemoglobin targets were associated with significant side effects such as access-site thrombosis,[52] strokes,[55] and

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possibly cardiovascular events.[54,55] Only the CREATE trial was able to demonstrate a quality-of-life benefit for the high-target group.[54]

It remains unclear whether these adverse events were from the therapy itself or from an increased morbidity burden in the treated patients. Erythropoietin use is associated with hypertension,[56] thought to be related to endothelin-mediated vasoconstriction.[57] In our experience, this is most evident when hemoglobin levels are normalized with ESA therapy. Cycling of erythropoietin levels between extreme levels can lead to vascular remodeling, which may also be related to its cardiovascular effects.[57]

A noticeable finding in several of these trials was that patients failed to achieve the higher hemoglobin target despite the use of very high doses of ESA. Reanalysis of data from the CHOIR and CREATE trials showed that the patients who had worse outcomes were more likely to have required very high doses without achieving their target hemoglobin.[58,59] Indeed, patients who achieved the higher target hemoglobin levels, usually at lower ESA doses, had better outcomes. This suggested that the need for a higher dose was associated with poorer outcomes, either as a marker of comorbidity or due to yet undocumented side effects of such high doses.

Before attributing anemia to chronic kidney disease, evaluate for a reversible process

General approach to therapy

Before attributing anemia to chronic kidney disease, a thorough evaluation should be conducted to look for any reversible process that could be contributing to the anemia.

The causes of anemia are numerous and beyond the scope of this review. However, among the common causes of anemia in chronic kidney disease are deficiencies of iron, vitamin B_{12}, and folate. Therefore, guidelines recommend checking iron, vitamin B_{12}, and folate levels in the initial evaluation of anemia.[60]

Iron deficiency in particular is very common in chronic kidney disease patients and is present in nearly all dialysis patients.[61] Hemodialysis patients are estimated to lose 1 to 3 g of iron per year as a result of blood loss in the dialysis circuit and increased iron utilization secondary to ESA therapy.[62]

However, in contrast to the general population, in which the upper limits of normal for iron indices are well defined, high serum ferritin levels appear to be poorly predictive of hemoglobin responsiveness in dialysis patients.[63,64] Thus, the cutoffs that define iron responsiveness are much higher than standard definitions for iron deficiency.[65,66] The Dialysis Patients' Response to IV Iron With Elevated Ferritin (DRIVE) study showed that dialysis patients benefit from intravenous iron therapy even if their ferritin is as high as 1,200 ng/mL, provided their transferrin saturation is below 30%.[67]

Of note, erythropoietin levels cannot be used to distinguish renal anemia from other causes of anemia. Indeed, patients with renal failure may have "relative erythropoietin deficiency," ie, "normal" erythropoietin levels that are actually too low in view of the degree of anemia.[68,69] In addition to the decreased production capacity by the kidney, there appears to be a component of resistance to the action of erythropoietin in the bone marrow.

For these reasons, there is no erythropoietin level that can be considered "inadequate" or defining of renal anemia. Thus, measuring erythropoietin levels is not routinely recommended in the evaluation of renal anemia.

Two ESA preparations

The two ESAs that have traditionally been used in the treatment of renal anemia are recombinant human erythropoietin and darbepoietin alfa. They appear to be equivalent in terms of safety and efficacy.[70] However, darbepoietin alfa has more sialic acid molecules, giving it a higher potency and longer half-life and allowing for less-frequent injections.[71,72]

In nondialysis patients, recombinant human erythropoietin is typically given every 1 to 2 weeks, whereas darbepoietin alfa can be given every 2 to 4 weeks. In dialysis patients, recombinant human erythropoietin is typically given 3 times per week with every dialysis treatment, while darbepoietin alfa is given once a week.

Target hemoglobin levels: ≤ 11.5 g/dL

In light of the four trials described in **Table 1**, the international Kidney Disease: Improving Global Outcomes (KDIGO) guidelines[60] recommend the following (**Table 2**):

For patients with chronic kidney disease

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TABLE 2

Target hemoglobin and iron indices

	Target hemoglobin	Target ferritin	Target transferrin saturation
Chronic kidney disease	> 10 g/dL	> 100 ng/mL	> 20%
End-stage renal disease	10–11.5 g/dL	200–1,200 ng/mL	30%–50%

Based on information in KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease. Kidney Int Suppl 2012; 2:279–335.

who are not on dialysis, ESA therapy should not be initiated if the hemoglobin level is higher than 10 g/dL. If the hemoglobin level is lower than 10 g/dL, ESA therapy can be initiated, but the decision needs to be individualized based on the rate of fall of hemoglobin concentration, prior response to iron therapy, the risk of needing a transfusion, the risks related to ESA therapy, and the presence of symptoms attributable to anemia.

For patients on dialysis, ESA therapy should be used when the hemoglobin level is between 9 and 10 g/dL to avoid having the hemoglobin fall below 9 g/dL.

In all adult patients, ESAs should not be used to intentionally increase the hemoglobin level above 13 g/dL but rather to maintain levels no higher than 11.5 g/dL. This target is based on the observation that adverse outcomes were associated with ESA use with hemoglobin targets higher than 13 g/dL (**Table 1**).

Target iron levels

Regarding iron stores, the guidelines recommend the following:

For adult patients with chronic kidney disease who are not on dialysis, iron should be given to keep transferrin saturation above 20% and ferritin above 100 ng/mL. Transferrin saturation should not exceed 30%, and ferritin levels should not exceed 500 ng/mL.

For adult patients on dialysis, iron should be given to maintain transferrin saturation above 30% and ferritin above 200 ng/mL.

The upper limits of ferritin and transferrin saturation are somewhat controversial, as the safety of intentionally maintaining respective levels greater than 30% and 500 ng/mL has been studied in very few patients. Transferrin saturation should in general not exceed 50%.

High ferritin levels are associated with higher death rates, but whether elevation of ferritin levels is a marker of excessive iron administration rather than a nonspecific acute-phase reactant is not clear. The 2006 guidelines[60] cited upper ferritin limits of 500 to 800 ng/mL. However, the more recent DRIVE trial[67] showed that patients with ferritin levels of 500 to 1,200 ng/mL will respond to intravenous administration of iron with an increase in their hemoglobin levels. This has led many clinicians to adopt a higher ferritin limit of 1,200 ng/mL.

Hemosiderosis, or excess iron deposition, was a known consequence of frequent transfusions in patients with end-stage renal disease before ESA therapy was available. However, there have been no documented cases of clinical iron overload from iron therapy using current guidelines.[73]

These algorithms are nuanced, and the benefit of giving intravenous iron should always be weighed against the risks of short-term acute toxicity and infection. Treatment of renal anemia not only requires in-depth knowledge of the topic, but also familiarity with the patient's specific situation. As such, it is not recommended that clinicians unfamiliar with the treatment of renal anemia manage its treatment.

Measuring erythropoietin is not routine in the evaluation of renal anemia

PARTICULAR CIRCUMSTANCES

Inflammation and ESA resistance

While ESAs are effective in treating anemia in many cases, in many patients the anemia fails to respond. This is of particular importance, since ESA hyporesponsiveness has been found to be a powerful predictor of cardiovascular events and death.[74] It is unclear,

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however, whether high doses of ESA are inherently toxic or whether hyporesponsiveness is a marker of adverse outcomes related to comorbidities.

KDIGO defines initial hyporesponsiveness as having no increase in hemoglobin concentration after the first month of appropriate weight-based dosing, and acquired hyporesponsiveness as requiring two increases in ESA doses up to 50% beyond the dose at which the patient had originally been stable.[60] Identifying ESA hyporesponsiveness should lead to an intensive search for potentially correctable factors.

The two major factors accounting for the state of hyporesponsiveness are inflammation and iron deficiency.[75,76]

Inflammation. High C-reactive protein levels have been shown to predict resistance to erythropoietin in dialysis patients.[77] The release of cytokines such as tumor necrosis factor alpha, interleukin 1, and interferon gamma has an inhibitory effect on erythropoiesis.[78] Additionally, inflammation can alter the response to ESAs by disrupting the metabolism of iron[79] through the release of hepcidin, as previously discussed.[38] These reasons likely account for the observed lower response to ESAs in the setting of acute illness and explain why ESAs are not recommended for correcting acute anemia.[80]

The upper limits of ferritin and transferrin saturation are controversial

Iron deficiency also can blunt the response to ESAs. Large amounts of iron are needed for effective erythropoietic bursts. As such, iron supplementation is now a recognized treatment of renal anemia.[81]

Other factors associated with hyporesponsiveness include chronic occult blood loss, aluminum toxicity, cobalamin or folate deficiencies, testosterone deficiency, inadequate dialysis, hyperparathyroidism, and superimposed primary bone marrow disease,[82,83] and these should be addressed in patients whose anemia does not respond as expected to ESA therapy. A summary of the main causes of ESA hyporesponsiveness, their reversibility, and recommended treatments is presented in **Table 3**.

Antibody-mediated pure red-cell aplasia. Rarely, patients receiving ESA therapy develop antibodies that neutralize both the ESA and endogenous erythropoietin. The resulting syndrome, called antibody-mediated pure red-cell aplasia, is characterized by the sudden development of severe transfusion-dependent anemia. This has historically been connected to epoetin beta, a formulation not in use in the United States. However, cases have been documented with epoetin alfa and darbepoetin. The incidence rate is low with subcutaneous ESA use, estimated at 0.5 cases per 10,000 patient-years[84] and anecdotal with intravenous ESA.[85] The definitive diagnosis requires demonstration of neutralizing antibodies against erythropoietin. Parvovirus infection should be excluded as an alternative cause of pure redcell aplasia.

ANEMIA IN CANCER PATIENTS

ESAs are effective in raising hemoglobin levels and reducing transfusion requirements in patients with chemotherapy-induced anemia.[86] However, there are data linking the use of ESAs to shortened survival in patients who have a variety of solid tumors.[87]

Several mechanisms have been proposed to explain this rapid disease progression, most notably acceleration in tumor growth[88–90] by stimulation of erythropoietin receptors on the surface of the tumor cells, leading to increased tumor angiogenesis.[91,92]

For these reasons, treatment of renal anemia in the setting of active malignancy should be referred to an oncologist.

NOVEL TREATMENTS

Several new agents for treating renal anemia are currently under review.

Continuous erythropoiesis receptor activator

Continuous erythropoiesis receptor activator is a pegylated form of recombinant human erythropoietin that has the ability to repeatedly activate the erythropoietin receptor. It appears to be similar to the other forms of erythropoietin in terms of safety and efficacy in both end-stage renal disease[93] and chronic kidney disease.[94] It has the advantage of an extended serum half-life, which allows for longer dosing intervals, ie, every 2 weeks. Its use is currently gaining popularity in the dialysis community.

HIF stabilizers

Our growing understanding of the physiology of erythropoietin offers new potential treat-

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TABLE 3

Erythropoiesis-stimulating agent hyporesponsiveness: A practical approach

Cause	Test	Course of action
Easily correctable causes		
Iron deficiency	Iron studies	If low, replenish
Vitamin B_{12} deficiency	Vitamin B_{12} level	If low, replenish
Folate deficiency	Folate level	If low, replenish
Hypothyroidism	Thyroid-stimulating hormone level	Manage hypothyroidism
ACEi/ARB-induced anemia	ACEi or ARB level	Stop ACEi or ARB
Potentially correctable causes		
Infection and inflammation	Serum C-reactive protein level	If elevated, check for and treat infection or inflammation
Hyperparathyroidism	Parathyroid hormone level	Manage hyperparathyroidism
Underdialysis	Kt/V	Improve dialysis efficiency
Blood loss or hemolysis	Reticulocyte count (look for high value)	Endoscopy, colonoscopy, hemolysis screen
Bone marrow disorder, pure red-cell aplasia	Reticulocyte count (look for low value)	Check anti-ESA antibodies, parvovirus polymerase chain reaction, consider bone marrow biopsy
Noncorrectable causes		
Hemoglobinopathies	Serum protein electrophoresis	Hematology referral
Bone marrow disorders	Bone marrow biopsy	Hematology referral

ACEi = angiotensin-converting enzyme inhibitor, ARB = angiotensin II receptor blocker, Kt/V = dialyzer clearance of urea times dialysis time, divided by volume of distribution of urea

ment targets. As previously described, production of erythropoietin is stimulated by HIFs. In order to be degraded, these HIFs are hydroxylated at their proline residues by a prolyl hydroxylase. A new category of drugs called prolyl-hydroxylase inhibitors (PDIs) offers the advantage of stabilizing the HIFs, leading to an increase in erythropoietin production.

In phase 1 and 2 clinical trials, these agents have been shown to increase hemoglobin in both end-stage renal disease and chronic kidney disease patients[15,16] but not in anephric patients, demonstrating a renal source of the erythropoietin production even in nonfunctioning kidneys. The study of one PDI agent (FG 2216) was halted temporarily after a report of death from fulminant hepatitis, but the other (FG 4592) continues to be studied in a phase 2 clinical trial.[95,96]

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TAKE-HOME POINTS

- Anemia of renal disease is a common condition that is mainly caused by a decrease in erythropoietin production by the kidneys.
- While anemia of renal disease can be corrected with ESAs, it is necessary to investigate and rule out underlying treatable conditions such as iron or vitamin deficiencies before giving an ESA.
- Anemia of renal disease is associated with significant morbidity such as increased risk of left ventricular hypertrophy, myocardial infarction, and heart failure, and has been described as an all-cause mortality multiplier.
- Unfortunately, the only undisputed benefit of treatment to date remains the avoidance of blood transfusions. Furthermore, the large randomized controlled trials that looked at the benefits of ESA have shown that their use can be associated with increased risk of cardiovascular events. Therefore, use of an ESA in end-stage renal disease should never target a normal hemoglobin levels but rather aim for a hemoglobin level of no more than 11.5 g/dL.
- Use of an ESA in chronic kidney disease should be individualized and is not recommended to be started unless the hemoglobin level is less than 10 g/dL.
- Several newer agents for renal anemia are currently under review. A pegylated form of recombinant human erythropoietin has an extended half-life, and a new and promising category of drugs called HIF stabilizers is currently under study.

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***ADDRESS**: James F. Simon, MD, Department of Nephrology and Hypertension, Q7, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; simonj2@ccf.org*

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***ADDRESS**: Natasha Atanaskova Mesinkovska, MD, PhD, Department of Dermatology and Dermatopathology, University of California Irvine, Gottschalk Medical PLaza, 1 Medical PLaza Drive, Irvine, CA 92697; natashadermatology@gmail.com*

CORRECTION

Anemia of chronic kidney disease

(AUGUST 2016)

The article "Anemia of chronic kidney disease: Treat it, but not too aggressively" by Drs. Georges Nakhoul and James F. Simon (Cleve Clin J Med 2016; 83:613–624) contained a typographical error. In **Table 2**, the target ferritin level in chronic kidney disease is given as greater than 100 ng/dL, and for end-stage renal disease 200 to 1,200 ng/dL. Ferritin levels are measured in ng/mL, not ng/dL.