Update on Anemia in ESRD and Earlier Stages of CKD: Core Curriculum 2018

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Anemia is a frequent complication during the later stages of chronic kidney disease. When present, it may cause symptoms such as fatigue and shortness of breath. The pathogenesis of anemia in chronic kidney disease is complex, but a central feature is a relative deficit of erythropoietin. New information has elucidated the critical role of the hypoxia-sensing system in mediating erythropoietin synthesis and release. Iron deficiency is a second important factor in the anemia of chronic kidney disease. New insights into the dynamics of iron metabolism have clarified the role of chronic inflammation and hepcidin as key mediators of impaired iron utilization. In this article, we review the epidemiology, pathobiology, clinical evaluation, and treatment of anemia in chronic kidney disease.

Complete author and article information provided before references.

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The Core Curriculum aims to give trainees in nephrology a strong knowledge base in core topics in the specialty by providing an overview of the topic and citing key references, including the foundational literature that led to current clinical approaches.

Case: *A 54-year-old man with diabetes mellitus, hypertension, and coronary artery disease is being treated for chronic kidney disease (CKD). His estimated glomerular filtration rate has declined over the past 2 years from 40 to 14 mL/min/1.73 m^2. The patient reports increased fatigue and asks about the causes of his anemia. Red blood cell indexes are normal, and iron test results and serum folate and vitamin B_{12} concentrations are found to be normal.*

Question 1: What is the most likely cause or causes of the patient's anemia?

a) Diabetes mellitus
b) Relative erythropoietin deficiency
c) Iron deficiency
d) Multiple myeloma

For answer, see Appendix.

Introduction

Kidney failure produces numerous changes that destabilize homeostasis. An important example is diminished erythropoiesis, with anemia being a common complication of kidney disease. The anemia that accompanies kidney failure was recognized by Sir Robert Christison in 1839, who observed that "by far the most remarkable character of the blood in the advanced stage of the Bright's disease is a gradual and rapid reduction of its colouring" and "no other natural disease came as close to hemorrhage for impoverishing the red particles of the blood." Similarly, Richard Bright had noticed that patients with kidney disease had paleness of the skin: "after a time, the healthy colour of the countenance fades."*

*Christison R. On Granular Degeneration of the Kidnies and Its connexions With Dropsy Inflammations and Other Diseases. Black, Edinburgh: 1839, pp. 63-74.

Anemia remains an important complication experienced by patients with kidney disease, although one that is treatable. The prevalence of anemia depends on its definition, but generally increases in frequency and severity in the more advanced stages of CKD. Studying adult patients at Boston health clinics, Hsu et al published in 2001 the fact that mean hematocrit (Hct) values decreased with creatinine clearance < 60 mL/min in men and <40 mL/min in women. More severe anemia (Hct < 33%) was common among patients with estimated glomerular filtration rates < 30 mL/min/1.73 m^2 in women and <20 mL/min/1.73 m^2 in men. Hsu et al published a separate study the next year that used the third National Health and Nutrition Examination Survey (NHANES III [1988-1994]). Among 15,971 adults, anemia as defined by hemoglobin (Hb) concentration < 12 g/dL in men and <11 g/dL in women was more common with creatinine clearances < 70 mL/min and <50 mL/min in men and women, respectively. A more significant mean decrease in Hb concentration of 1.0 g/dL was found for patients with creatinine clearances < 30 mL/min.

Among patients with diabetes mellitus and CKD, anemia tends to be more severe and to develop at an earlier point in CKD. El-Achkar et al studied 5,380 individuals who were surveyed as part of the National Kidney Foundation's Kidney Early Evaluation Program (KEEP), a community-based screening program for patients at higher risk for kidney disease. Using a definition of anemia as Hb concentration < 12 g/dL in men and in women older than 50 years and <11 g/dL in women 50 years and younger, the prevalence was greater among patients with CKD with diabetes (Fig 1). In patients with stage 3 CKD, 22.2% of patients with diabetes were anemic, increasing to 52.4% in

stage 4 CKD. The difference in prevalence between those with and without diabetes was greatest in stage 3 CKD, for which the rate of anemia was 3 times as high among the former. Erythropoietin deficiency is the most common cause of anemia in CKD, and the deficiency may be more severe in patients with diabetes. In a study of 694 anemic patients, Symeonidis et al observed that serum erythropoietin concentrations, in relation to anemia severity, were lower in patients with diabetes.

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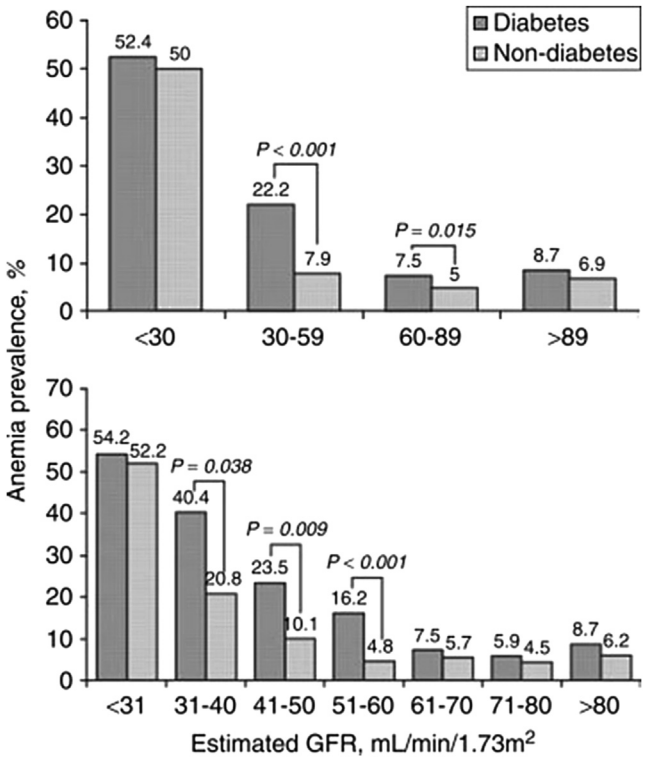

Figure 1. Prevalence of anemia (hemoglobin < 12 g/dL in men and <11 g/dL in women) in patients with or without diabetes. Abbreviation: GFR, glomerular filtration rate. Reproduced from El-Achkar et al (*Kidney Int.* 2015;67:1483-1488) with permission of the copyright holder (International Society of Nephrology).

Question 2: Which factor is most responsible for sensing cellular hypoxia?

a) Erythropoietin
b) Hepcidin
c) Hypoxia-inducible factor (HIF)-prolyl hydroxylase
d) Fibroblast growth factor 23
e) Ferroportin

For answer, see Appendix.

Physiology/Pathophysiology

Background

The erythropoietic system maintains homeostasis in the red blood cell supply to achieve adequate tissue oxygen delivery. Balance is achieved by replacing erythrocytes lost due to senescence and bleeding (if the blood loss is not severe). In addition, it has long been known that hypoxia stimulates new erythrocyte production. Hypoxia could be due to pulmonary disease, reduced tissue perfusion, or living at high altitude. The expectation that a circulating factor governed the erythropoietic response was followed by the discovery of erythropoietin and the cloning of its gene in 1985. Soon thereafter, the mechanism by which cells sensed hypoxia and the central role of the transcriptional factor, hypoxia inducible factor 1 (HIF-1), was identified.

Tissue oxygen availability is sensed continually at the cellular level. If hypoxia is detected, a multifaceted response is triggered. An important component of the response is increased production of the glycoprotein hormone erythropoietin. This 30.4-kDa molecule is the key stimulus for erythrocyte production in mammals. It acts as a true hormone in that it is produced in the kidneys and circulates and acts at tissue receptors throughout the body, most importantly in bone marrow. Erythropoietin binds to its marrow cell-surface receptors to stimulate erythropoiesis.

Hypoxia Sensing: The HIF System

The body's sensing of tissue hypoxia, and thereby recognition of anemia, occurs by the HIF system (Fig 2). Central to this function are 2 proteins, HIF-α and HIF-β. HIF-α is continually produced, but when sufficient oxygen is present, it is rapidly "marked" (hydroxylated) for degradation by enzymes, the HIF-prolyl hydroxylases. The prolyl hydroxylases work as oxygen sensors because they require oxygen as a co-substrate. After hydroxylation, HIF-α is recognized by the von Hippel-Lindau protein, polyubiquitinated, and destroyed. HIF-β is constitutively expressed, but is not sensitive to hypoxic degradation. When tissue hypoxia occurs, HIF-α accumulates, translocates to the nucleus, forms a heterodimer with HIF-β, and binds to hypoxia response elements of a large number of oxygen-sensitive genes. One of these is the erythropoietin gene, leading to increased erythropoietin production. Numerous other genes, including those coding for enzymes

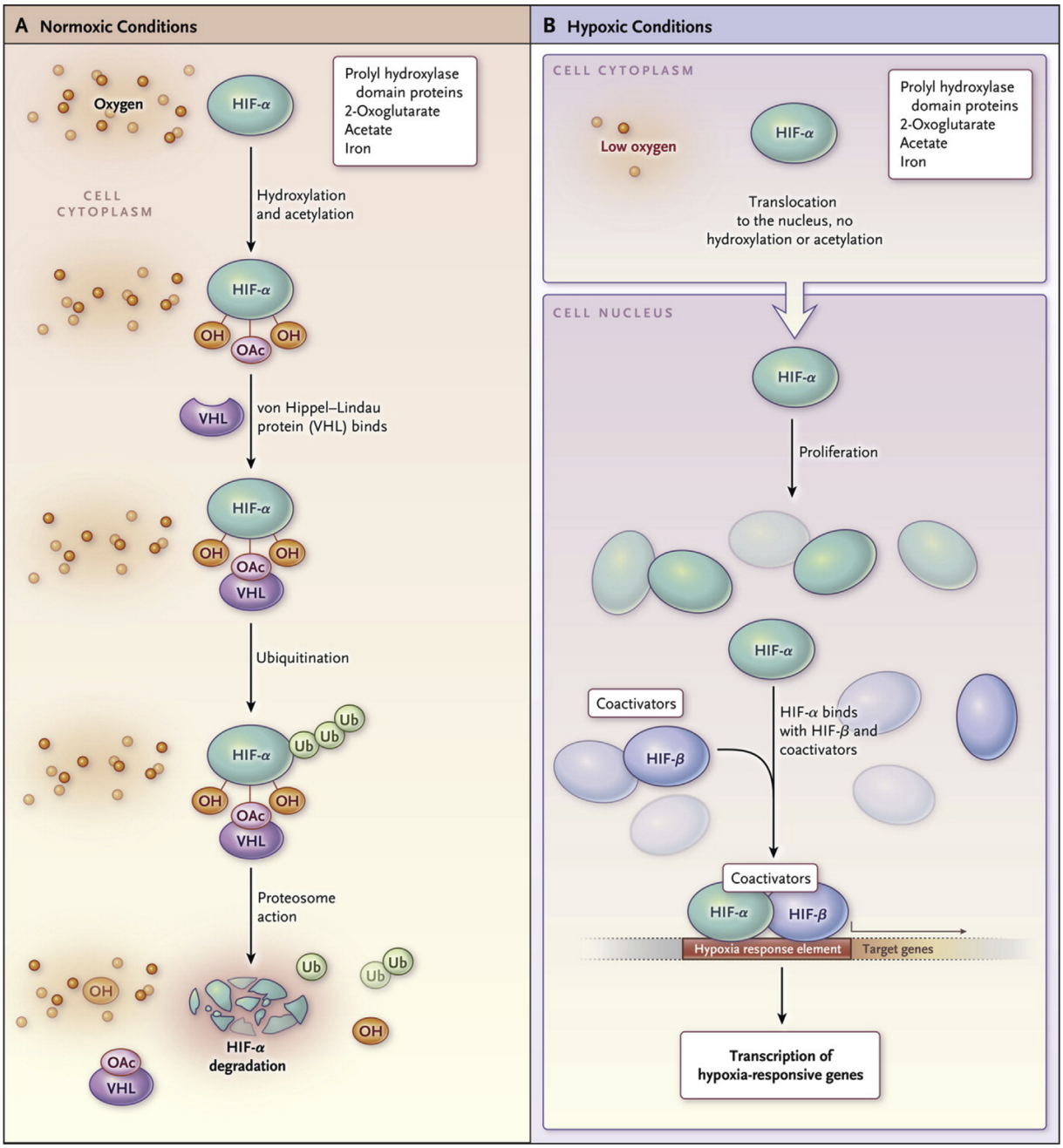

Figure 2. Under normoxic conditions, hypoxia inducible factor (HIF)-α is hydroxylated by prolyl hydroxylase domain proteins and then undergoes proteosomal degradation. Under hypoxic conditions, HIF-α does not undergo degradation, translocates to the nucleus, binds with HIF-β, and activates the hypoxia response element, initiating gene transcription of erythropoietin. Reproduced from West (*NEJM*. 2017;376:1965-1971) with permission of the copyright holder (Massachusetts Medical Society).

and transporters involved with iron metabolism, angiogenesis, and mitochondrial genesis, are also stimulated.

There are currently 3 forms of HIF-α that have been identified, HIF-1α, HIF-2α, and HIF-3α. It is unclear how diverse the differential transcriptional response to these forms might be. There are many shared targets of HIF-1 and HIF-2, but certain genes are regulated more by one or the other. Most relevant to the current discussion, HIF-2 appears to play a greater role in the regulation of erythropoietin production and activation of iron metabolism genes. This differential effect provides a potential therapeutic opportunity to target one or the other HIF molecules. Small-molecule inhibitors of prolyl hydroxylases, which in effect stabilize HIF-α, are currently being studied for the potential treatment of anemia in patients with CKD. By stimulating the production of erythropoietin and iron-regulatory proteins, a concerted approach to anemia treatment may be achievable.

Erythropoietin

Erythropoietin is a highly glycosylated molecule of 165 amino acids. The amino acid sequence is important for receptor binding, while the 4 carbohydrate chains affect the molecule's metabolism. Based on detection of messenger RNA transcripts coding for erythropoietin, production occurs primarily in renal cortical interstitial cells in adults. A secondary minor source of erythropoietin production is the liver. Interestingly, in the absence of the kidneys, hepatic erythropoietin production can increase significantly.

Following synthesis, erythropoietin is secreted directly into the bloodstream; there is no storage within the cells in which it is produced. When in circulation, the volume of distribution approximates that of the plasma volume space. Recombinant erythropoietin, and presumably native erythropoietin, circulates with a half-life of approximately 5 to 12 hours.

Erythropoietin quantities are traditionally expressed as units, with 1 unit representing the erythropoietic effect of stimulation with 5 μmol of cobalt chloride. Under basal conditions, serum erythropoietin concentration is steady and present at low levels (10-30 U/L). In the presence of anemia, serum erythropoietin can increase sharply to concentrations that can exceed 1,000 U/L. It should be noted that erythropoietin concentrations vary according to the assay used. Older assays had a normal range of 10 to 30 U/L. More recent assays have been reported to vary from about 2 to 4 U/L for the lower limits to 12 to 18 U/L for upper limits.

The action of erythropoietin occurs after its interaction with the erythropoietin receptor, present in highest quantities on the cell membranes of bone marrow erythroid precursor cells. The receptors appear to be dimers, but after binding of the ligand erythropoietin, there is a conformational change in the receptor's homodimeric structure. This activated erythropoietin-receptor interaction results in a critical cascade of signal transduction (this pathway is reviewed in depth by Richmond et al). The result is increased cell division and enhanced survival of red blood cell precursors. This is particularly true for erythroid progenitors known as BFU-E and CFU-E (burst forming unit- and colony forming unit-erythroid, respectively), which express high cell-surface concentrations of erythropoietin receptors. Remarkably, after binding to its receptor, erythropoietin rapidly disappears, indicating that cellular internalization may be one mechanism of erythropoietin (and erythropoiesis) downregulation.

Iron and Hepcidin

Effective erythropoiesis is dependent on adequate availability of both erythropoietin and iron. Iron deficiency is common in patients with CKD, occurring in ≥50% of patients with non–dialysis-dependent CKD and a greater percentage of patients receiving dialysis. The reasons for iron deficiency include occult blood loss, infection, systemic inflammatory conditions, surgical procedures, venipuncture, impaired absorption secondary to elevated hepcidin concentrations, and in dialysis, retention of blood by the dialysis apparatus. It is estimated that hemodialysis patients may lose ≥2,000 mg of iron per year as a result of these factors. The magnitude of iron loss in non–dialysis-dependent CKD is unclear.

The deficiency of iron available for erythropoiesis in CKD is frequently compounded by a relative block in iron absorption from the intestines and reduced iron release from storage in macrophages and the liver. This iron blockade phenomenon is mediated by the master regulator of iron homeostasis, the liver-produced circulating protein hepcidin. Elevated hepcidin concentrations cause the cellular iron transporter ferroportin to be internalized into cells. The result is that iron does not enter the circulation through enterocytes or from storage tissues. Hepcidin concentrations increase in response to increased iron storage in the body and decrease when iron deficiency is present. A secondary, but important, cause of increased hepcidin concentration is inflammation. This response limits the availability of iron to microorganisms during infection. In patients with CKD, it may often be a maladaptive response. An occult state of inflammation increases the hepcidin concentration and blocks iron available for erythropoiesis. This can sometimes be recognized by the fairly common finding in hemodialysis patients of reduced transferrin saturation (TSAT; decreased circulating iron) occurring at the same time that the serum ferritin concentration is discordantly increased (elevated iron storage). The frequent presence of inflammation in CKD results in iron-restricted erythropoiesis due to hepcidin effects, but often superimposed on underlying true iron deficiency.

Erythropoiesis in CKD

Among patients with CKD, there is a relative deficiency in erythropoietin production, and this is the main reason that anemia develops. Other factors that may contribute include iron deficiency, blood loss, inflammation, hemolysis, and nutritional deficits (Box 1). However, the central role of erythropoietin deficiency is well documented and best demonstrated by the consistent and robust improvement in Hb concentrations after treatment with recombinant human erythropoietin (rHuEPO). Surprisingly, serum erythropoietin concentration is often not reduced in CKD, except in relation to the degree of anemia present. However, as kidney failure progresses, erythropoietin deficiency becomes more pronounced and the decline in serum concentrations parallels kidney excretory functional loss.

In addition to experiencing diminished erythrocyte production, patients with CKD may also have shortened red blood cell survival. Ma et al recently studied 54 hemodialysis patients and found mean red blood cell survival to be only 73.2 ± 17.8 days. Similarly, Sato et al found

Box 1. Common Causes of Anemia in CKD

- Relative erythropoietin deficiency
- Iron deficiency
- Blood loss
- Reduced erythrocyte survival duration
- Inflammation
- Infection
- Underlying hematologic disease
- Hyperparathyroidism (dialysis patients)
- Hemolysis
- Nutritional deficits

Abbreviation: CKD, chronic kidney disease.

erythrocyte lifespan to be 89 ± 28 days. The cause of shortened red blood cell survival in CKD remains incompletely understood, but blood loss from the dialysis procedure is one contributing factor.

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Symptoms and Outcomes Related to Anemia in CKD

Impact of Anemia on Symptoms/Quality of Life

Anemia results in reduced oxygen delivery to the body's organs and tissues, making symptoms such as fatigue, shortness of breath, insomnia, headaches, and reduced mental acuity common. It should be noted that these nonspecific symptoms could also be due to uremia and other causes. Fatigue may develop slowly as anemia progresses, and patients may not be fully aware of how their lives have been affected. Focused questioning often reveals restricted activity in compensation for reduced functional capacity.

An extension of anemia-related symptoms is the overall impact on patients' quality of life. Not unexpectedly, patients receiving dialysis often have significantly diminished quality of life due to existing comorbid conditions and/or the dialysis procedure itself. Before the availability of rHuEPO treatment, severe anemia was common among patients receiving dialysis, with Hb often in the range of 6 to 9 g/dL. Nephrologists who treated patients in the pre-rHuEPO era, when severe anemia was common, observed that anemia significantly degraded many patients' quality of life. However, in the pre-rHuEPO era, there were few studies of the actual impact of anemia. One exception was a study of 1,013 hemodialysis patients reported by Moreno et al, who used the Karnofsky scale and Sickness Impact Profile to assess quality of life and function. The most striking finding was that 26% to 31% of patients had severely diminished scores on the Karnofsky scale. Aspects of impaired function included work, recreation, home management, and sleep. Notably, lower Hb concentration was strongly associated with diminished quality of life. Like all associations, this does not prove that anemia is the cause of diminished quality of life.

Impact of Anemia on Mortality Risk

Among patients with CKD, for whom cardiovascular comorbid conditions are common, it is a reasonable

hypothesis that reduced carriage of oxygen to tissues could contribute to mortality risk. Observational studies have consistently demonstrated a strong association between lower Hb concentrations in dialysis patients and increased risk for death. Ma et al performed a study of 96,369 hemodialysis patients, finding that lower baseline Hct was associated with higher mortality risk. For Hct < 27%, the relative risk for death was 1.33 compared with patients with Hct of 30% to 33%. Sandgren et al studied mortality risk in Medicare beneficiaries and found that patients with CKD and anemia have a 270% increase in 2-year mortality compared with patients without these diagnoses. Several other studies also concluded that lower Hb concentrations in CKD are associated with increased risk for mortality. It is important to note that in contrast to these observational studies, interventional trials have failed to find that rHuEPO treatment, generally to near-normal Hb concentrations, improves mortality risk. Rather, the trials designed to increase Hb to near-normal concentrations (>13 g/dL) have found increased risk for mortality and cardiovascular complications. This leaves the question of causality in the relationship of anemia to increased mortality risk unresolved.

Impact of Anemia on Left Ventricular Hypertrophy

There is a great burden of cardiac disease in patients with CKD. It is highly plausible that anemia, by increasing the work of the heart and reducing tissue oxygen delivery, could exacerbate cardiac injury. The most definitive relationship between anemia and heart disease is the development of left ventricular hypertrophy (LVH). For example, Foley et al found LVH to be present in 73.9% of patients new to dialysis therapy. This is important because LVH is strongly and independently associated with increased mortality risk. In addition, the stiffened left ventricle is functionally sensitive to blood volume changes. This results in heightened risk in dialysis patients for both pulmonary edema and intradialytic hypotension, depending on volume status.

The relationship between anemia and LVH in CKD has been studied by several investigators. Silberberg et al analyzed a cohort of 78 hemodialysis patients. A strong association was demonstrated between worsening anemia and LVH. Among patients in the lowest quartile of Hb concentrations, mean left ventricular mass index was ~30% higher than in the highest quartile. Levin et al studied 175 patients with non–dialysis-dependent CKD. LVH was found in 38.9% of patients. There was an association with anemia; each 1-g/dL lower Hb concentration was associated with 6% greater LVH. Early rHuEPO intervention studies, often underpowered, hinted at the potential of treatment to induce regression of LVH. In contrast, larger well-powered randomized controlled trials have generally found no benefit to anemia correction with rHuEPO for improvement or slowing of LVH.

Other Effects of Anemia in CKD

There has been interest in whether anemia might hasten the progression of kidney disease by depriving the kidneys of needed oxygen. An analysis of the RENAAL (Reduction of Endpoints in NIDDM With the Angiotensin II Antagonist Losartan) trial sought to address the issue. The primary purpose was to evaluate losartan compared to conventional antihypertensive treatment for renal and other outcomes in patients with type 2 diabetes. Mohanram et al, in a post hoc analysis, found that among 1,513 participants, initial Hb concentration was a significant predictor of time to dialysis therapy and doubling of serum creatinine concentration. For every 1-g/dL decrease Hb concentration, there was 11% greater chance of these dual renal outcomes. However, because anemia becomes more prevalent as kidney function declines, it is unclear which is the cause and which is the effect: does anemia hasten kidney function decline or does anemia simply become more frequent with diminished kidney function? Although Mohanram and colleagues adjusted for a number of potential confounding variables, there remained a high risk for residual confounding. In contrast to the RENAAL study, TREAT (Trial of Darbepoetin Alfa in Type 2 Diabetes and Chronic Kidney Disease) found different results. More than 4,000 patients with type 2 diabetes were randomly assigned to treatment with darbepoetin alfa or placebo. Patients in the darbepoetin group were treated to a target Hb concentration of 13 g/dL; in the placebo group, treatment was reserved for patients with worsening anemia. More than 600 patients in the study progressed to end-stage renal disease. Importantly, there was no significant reduction in the rate of kidney failure in the darbepoetin alfa group compared to placebo. A meta-analysis of erythropoiesis-stimulating agent (ESA) intervention trials in CKD was reported by Elliott et al; these investigators found no benefit to ESA treatment with respect to kidney disease progression.

Although there are other adverse effects of anemia, a more detailed discussion is beyond the scope of the current article. We conclude our discussion of the impact of anemia in kidney disease by reminding the reader that in our view, the clearest detrimental effect is the diminution of life experience due to anemia-related symptoms such as fatigue.

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Case: *A 76-year-old woman with diabetes mellitus and stage 4 CKD is evaluated for progressive anemia. Blood test results are notable for the following values: serum potassium, 5.5 mEq/L; serum creatinine, 3.2 mg/dL; and serum calcium, 12.6 mg/dL. Hb concentration is 7.5 g/dL with normal erythrocyte indexes. Serum ferritin concentration is 358 ng/mL and TSAT is 20.2%.*

Question 3: In addition to erythropoietin deficiency, what other cause of anemia is important to exclude in this case?

a) Iron deficiency
b) Hyperparathyroidism
c) Malignancy
d) Hypothyroidism
e) Endocarditis

For answer, see Appendix.

Diagnostic Evaluation

The World Health Organization defines anemia as Hb concentration < 12.0 g/dL in women and <13.0 g/dL in men. In our opinion, in non–dialysis-dependent CKD, the nephrologist should take an active role in management when Hb concentration decreases to <12 g/dL. The diagnosis of anemia does not imply that rHuEPO treatment should necessarily be initiated, but rather that evaluation and ongoing monitoring are necessary.

The initial evaluation of anemia in CKD involves a targeted clinical assessment. Although relative erythropoietin deficiency will usually be the most important causal element, other contributing factors should be considered. A focused history, physical examination, and laboratory review should be conducted (Box 2). The goal is similar to anemia evaluation in patients without kidney disease: a broad search for signs of reduced erythrocyte production, hemolysis, sequestration, and bleeding. In patients with CKD, special emphasis should be placed on testing for iron deficiency and occult blood loss because of their frequent occurrence in this population.

We would suggest that blood testing include a complete blood cell count with red blood cell indexes. Abnormal leukocyte or platelet counts should suggest the possibility of a more generalized bone marrow disorder. Erythrocytic microcytosis or macrocytosis helps point to factors other than erythropoietin deficiency that may be contributing to anemia. A reticulocyte count may help to better understand the appropriateness of the bone marrow's response to anemia. One test that is not advised in the anemia evaluation is measurement of serum erythropoietin. Because the deficiency is relative, test results rarely help in the evaluation or subsequent management.

Other causes for anemia may become apparent during evaluation. Symptoms of bone pain and a low anion gap may suggest the need to evaluate for a dysproteinemic state. Heavy menstrual bleeding may suggest gynecologic pathology such as fibroid tumors of the uterus. A diet low in leafy vegetables or high mean erythrocyte cell volume could suggest folic acid deficiency. Progressive weight loss might indicate a need to evaluate for malignancy. An enlarged spleen found on physical examination may suggest a primary hematologic disease.

Because of the frequency of iron deficiency in this population, iron indexes should be assessed in all patients with CKD and anemia. The most commonly used iron tests are measurement of serum ferritin and TSAT. The former reflects primarily on the body's stores of iron. In patients with CKD, serum ferritin concentrations are often increased independent of iron status by the presence of

Box 2. Evaluation of Anemia in CKD

- Focused history and physical examination
- Blood testing
  - ◇ Chemistries
  - ◇ Complete blood cell count (including red blood cell indexes)
  - ◇ Reticulocyte count
  - ◇ Serum ferritin
  - ◇ Transferrin saturation
  - ◇ Folic acid
  - ◇ Vitamin B_{12}

Abbreviation: CKD, chronic kidney disease.

inflammation, requiring a more holistic approach to diagnosis. TSAT is a measure of circulating iron. Plasma total iron bound to transferrin varies from 2 to 4 mg, whereas the daily need for iron in bone marrow is much higher, necessitating rapid turnover of iron from tissue stores and transport to the bone marrow.

In the general population, either serum ferritin concentration < 30 ng/mL or TSAT < 15% are strongly suggestive of iron deficiency. However, both iron tests tend to be inaccurate for the diagnosis of iron deficiency in patients with CKD. The results of both tests reflect not only iron status, but also other factors that limit the ability to gauge iron status. In hemodialysis patients, there is no level of either test that optimizes both sensitivity and specificity. For example, TSAT < 21% comes closest to reasonable accuracy, with sensitivity of 81% for predicting response to intravenous (IV) iron, but with specificity of only 63%. Using the tests together and review of trends may help improve diagnostic utility. Among hemodialysis patients, iron deficiency is likely with serum ferritin concentration < 300 ng/ml or TSAT < 20%. In non–dialysis-dependent CKD, iron deficiency is probably present with serum ferritin concentrations < 100 ng/mL or TSAT < 15%. However, it must be recognized that iron deficiency may still be present in both populations with considerably higher values of either test.

Other tests have been used in the assessment of iron status. Reticulocyte Hb content (CHr) is a test that leverages the short circulating life of reticulocytes. Because the cells are detectable in the bloodstream for only approximately 24 hours, their Hb/iron content is a "snapshot" reflection of very recent iron status. Studies have found good diagnostic utility, but the lack of widespread availability has limited its use. Another test, the percentage of hypochromic red blood cells, has been demonstrated to have good utility as long as blood is processed fairly soon after sampling. This test, like CHr, has failed to enter mainstream clinical use.

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Case: *A 28-year-old woman with systemic lupus initiates hemodialysis treatment after a long course of various immunoregulatory treatments. As she begins dialysis therapy, epoetin alfa treatment is started as well, with an Hb concentration of 7.1 g/dL. The Hb concentration increases over 2 months to 9.8 g/dL but fails to increase further despite subsequent increases in her epoetin dose. She reports continued fatigue. Her lupus is inactive by symptoms and serologic test results. Erythrocyte indexes are normal, serum ferritin concentration is 26 ng/mL, and TSAT is 13.7%.*

Question 4: What would be the next step in anemia treatment?

a) Increase lupus treatment drugs
b) Increase dialysis time
c) Increase the epoetin dose further
d) Change to peritoneal dialysis
e) Treat with IV iron

For answer, see Appendix.

Treatment of Anemia in CKD

Introduction

The cornerstone of anemia treatment in CKD is rHuEPO therapy. Up to this point in the article, we have used the term rHuEPO as an indication of treatment with erythropoietin analogues. At the time of writing, new drugs that are not erythropoietin analogues are in development to stimulate erythropoiesis. The broader term that encompasses all these drugs is ESAs. In this section on anemia treatment, we use the broader term ESA as the term for all drugs, including erythropoietin analogues that stimulate erythropoiesis.

Treatment with ESAs should ideally be withheld until a preliminary anemia evaluation has been completed. There is little to be gained from treatment with these drugs in a patient who has iron deficiency or occult bleeding. If emergency anemia treatment is required in a patient who is actively bleeding or has a rapid decrease in Hb concentration, blood transfusion should be considered.

Iron Treatment

Before initiating ESA treatment, iron status should be assessed, as discussed. Iron treatment may be required before, during, or at times instead of ESA therapy. KDIGO (Kidney Disease: Improving Global Outcomes) recommendations for when to initiate iron treatment in CKD are listed in Box 3. There is a wide choice of both oral and IV iron agents available for treatment. Oral agents are generally ineffective for hemodialysis patients and only modestly effective in non–dialysis-dependent CKD. One exception is the oral iron phosphate binder ferric citrate, which is highly efficacious as an iron supplement in both patient populations. It is unclear why this oral iron agent is able to deliver iron to a greater extent than other forms of

Box 3. KDIGO Guideline Recommendations for When to Treat With Iron in CKD

2.1.2: For adult CKD patients with anemia not on iron or ESA therapy we suggest a trial of IV iron (or in CKD ND patients alternatively a 1–3 month trial of oral iron therapy) if (*2C*):
- an increase in Hb concentration without starting ESA treatment is desired* and
- TSAT is ≤30% and ferritin is ≤500 ng/ml (500 μg/l)

2.1.3: For adult CKD patients on ESA therapy who are not receiving iron supplementation, we suggest a trial of IV iron (or in CKD ND patients alternatively a 1–3 month trial of oral iron therapy) if (*2C*):
- an increase in Hb concentration** or a decrease in ESA dose is desired*** and
- TSAT is ≤30% and ferritin is ≤500 ng/ml (500 μg/l)

*Based on patient symptoms and overall clinical goals, including avoidance of transfusion, improvement in anemia-related symptoms, and after exclusion of active infection.
**Consistent with Recommendations #3.4.2 and 3.4.3.
***Based on patient symptoms and overall clinical goals including avoidance of transfusion and improvement in anemia-related symptoms, and after exclusion of active infection and other causes of ESA hyporesponsiveness.

Abbreviations: CKD, chronic kidney disease; ESA, erythropoiesis-stimulating agent; IV, intravenous; Hb, hemoglobin; KDIGO, Kidney Disease: Improving Global Outcomes; ND, nondialysis; TSAT, transferrin saturation.

oral iron and without an apparently greater burden of side effects. In dialysis patients, when used as a phosphate binder, the drug will result in significant increases in iron parameters and potentially improves ESA response.

In contrast to oral forms of iron, IV iron is generally highly efficacious. It is a standard-of-care treatment for hemodialysis patients. Among these patients, the most commonly used agent in the United States is iron sucrose, usually administered at 50 to 100 mg/wk as needed. Other forms of IV iron are available, including iron dextran, ferric gluconate, ferumoxytol, ferric carboxymaltose, and iron isomaltoside. The great preponderance of iron sucrose use in the United States probably reflects market forces more than any specific drug properties. All these drugs are effective, and all probably carry some minor risk for hypotension or hypersensitivity reactions. The major difference is that a larger amount of iron can be administered at a single administration with iron dextran, ferumoxytol, ferric carboxymaltose, and iron isomaltoside compared with iron sucrose and ferric gluconate.

In hemodialysis, access to the circulation is simple, by patients' dialysis lines, and the available drugs are well tolerated. There are 3 strategies for IV iron administration in these patients. The first strategy is a repletion approach. Testing is performed for iron deficiency every 1 to 3 months. If iron deficiency is detected, a short course of IV iron is administered. A typical course would be 1,000 mg of iron sucrose or ferric gluconate over 10 to 12 dialysis treatments. A second approach might be termed maintenance therapy. In anticipation of blood loss, a weekly dose of IV iron is administered. A third method, administering large amounts of iron in a single dose, is not widely used in hemodialysis. There is no great evidence to support one IV iron method over the other. Given the marked difference between the mentioned uses of IV iron, other strategies could be used as well.

In patients with non–dialysis-dependent CKD or those treated with peritoneal dialysis, IV iron use is complicated by the need to establish IV access. Because of this, patients may be initiated on oral iron agents instead of or before treatment with IV iron. When IV iron is used in these patients, there should be appropriate observation for the development of hypotension or hypersensitivity reactions. In addition, in both these patient populations, care should be taken to preserve veins that may later be needed to create vascular access for hemodialysis.

IV iron treatment is highly efficacious, but at the time of this writing, its safety has not been fully evaluated. As a result, clinicians are not able to fully consider the balance of benefit and risk when making treatment decisions. The KDIGO recommendations help ensure effective treatment while avoiding potential risks (Box 3). One safety concern has been the possibility that IV iron could make iron more available to bacteria and other microorganisms. Because of this, we would suggest that IV iron not be administered during acute infections, especially when bacteremia is present. Treatment of iron deficiency can always be safely postponed until after an infection is fully treated.

ESA Treatment

Treatment with ESAs is the hallmark of anemia therapy in CKD. At the time of writing, all available ESAs are analogues of erythropoietin (Table 1). The first available was epoetin alfa, approved by the US Food and Drug Administration (FDA) in 1989 (only 5 years after cloning of the erythropoietin gene). Epoetin alfa is similar to native erythropoietin and is produced by recombinant DNA technology in massive cell cultures. The second ESA developed was darbepoetin alfa, which differs from native erythropoietin by 5 amino acids and by additional carbohydrate content that changes the pharmacokinetics, resulting in an extended serum half-life (approximately 2-3 times longer than epoetin alfa). A third ESA is methoxy polyethylene glycol-epoetin beta, which has a significantly increased serum half-life (Table 1). Less-frequent dosing is the expected advantage of an ESA with a longer half-life. Although

Table 1. Plasma Half-Lives of Erythropoietin Analogues

	Half-Life, h	
	Intravenous Administration	Subcutaneous Administration
Epoetin alfa	6.8	19.4
Darbepoetin alfa	25.3	48.8
Methoxy polyethylene glycol-epoetin beta	130	133

Note: Epoetin alfa, US trademarks, Epogen, Procrit; darbepoetin alfa, US trademark, Aranesp; and methoxy polyethylene glycol-epoetin beta, US trademark, Mircera.

this benefit is most evident in patients with non–dialysis-dependent CKD with anemia, it could have advantages in the dialysis facility, specifically with respect to freeing nurses to dedicate more time to patient assessment and education. However, the serum half-life of ESAs may not always correlate with required dose frequency. A recent Cochrane review of 14 randomized controlled trials concluded that short-acting ESAs for patients with non–dialysis-dependent CKD given at higher doses for extended intervals (2 or 4 weeks) were noninferior to more frequent dosing intervals in achieving and maintaining Hb concentrations.

Recommendations for initiation and maintenance therapy with ESAs from the KDIGO guideline are provided in Box 4. Initial suggested starting doses are listed in Table 2. These doses may not correlate exactly with FDA prescribing instructions; they reflect the opinions of the authors. Before starting treatment, iron status should be optimized and blood pressure optimally controlled.

After initiating treatment with an ESA, Hb concentration should be measured weekly until Hb stability and goals are achieved. A reasonable goal is an increase of 1 g/dL in Hb concentration within the first month of treatment. If the increase in Hb concentration is excessive (>1 g/dL over 2 weeks), the ESA dose should be reduced by 25% to 50%. As Hb concentration increases, blood pressure response should be monitored because blood pressure will increase during treatment in some patients. We recommend checking iron status monthly during initial ESA treatment. As the Hb concentration increases, a large amount of iron is transferred from storage tissues to the developing erythron, and iron deficiency is frequently induced. This may limit the effectiveness of ESA treatment.

The target Hb concentration during ESA treatment is controversial. The target should reflect a balancing of benefits and risks as applied to the individual patient. Some considerations and the supporting key studies are discussed next.

The benefits of ESA treatment are clear; avoidance of blood transfusions and improvement in anemia-related symptoms. Before the availability of ESAs, blood transfusions were frequently required by dialysis patients. Before the availability of ESAs, Hb concentrations of hemodialysis patients were often <8 g/dL. Although the blood supply in 2017 is generally considered safe, there are still certain risks and resource considerations associated with transfusion. Moreover, immune sensitization may limit the ability of patients to undergo eventual kidney transplantation. The ability of ESA treatment to reduce transfusions has been well demonstrated by placebo-controlled randomized trials. From the initial clinical study of rHuEPO in 1987, Eschbach et al noted, "Of 18 patients receiving effective doses of recombinant human erythropoietin, 12 who had required transfusions no longer needed them."[p. 73] Many subsequent studies have demonstrated a transfusion-sparing effect. Interestingly, during a more recent period when mean Hb concentrations decreased in dialysis patients (2010-2012), the rate of monthly blood transfusions increased from 9% to 11%.

As discussed in an earlier section, the symptoms of anemia can improve markedly with ESA treatment. This was easiest to observe in the initial clinical trials of epoetin, in which patients entered studies with very low Hb concentrations, usually <8 g/dL. For example, Delano et al studied 37 hemodialysis patients treated with ESAs, with the mean Hct increasing from 19.8% to 31.5%. Eighty-four percent of patients experienced an improved sense of well-being. In addition, improvements were found in appetite (81%), sexual function (62%), socializing (70%), and sleep (68%). In another study, The Canadian Erythropoietin Study Group randomly assigned 118 patients to treatment with placebo, low-dose ESA, or high-dose ESA. After 6 months of follow-up, mean Hb concentration in the placebo group was 7.4 g/dL. In ESA-treated groups, there was an improvement of 3 to 4 g/dL. ESA-treated patients experienced significant reduction in fatigue and improvement in several facets of quality of life. The Cooperative Multicenter EPO Clinical Trial Group studied 333 hemodialysis patients with baseline Hcts of 22.2%. The first follow-up for symptoms and functional capacity was assessed at a mean of 4.4 months, at which time mean Hct had increased to 35%. The number of patients free of physical limitations increased from 27% to 47.6%. The number of patients reporting that they were very active increased from 19.8% to 35.5%. At baseline, 26.7% of patients felt full of energy, which increased to 52.7% at follow-up.

In contrast to partial correction of severe anemia, there is less clarity as to whether ESA treatment to full Hb concentration normalization results in further increments in quality of life. More importantly, both cardiovascular and thromboembolic safety risks have become apparent. There are 4 major studies that have helped definitively demonstrate the general lack of benefit and increased risk with full Hb concentration normalization.

Besarab et al performed a randomized controlled trial of 1,233 hemodialysis patients. Epoetin alfa was used in both groups to target an Hct of 30% or 42% for 29 months. At the end of the study, there was no clear benefit of the higher Hct target. However, there was a strong trend toward increased mortality risk.

Drueke et al randomly assigned 603 patients with non–dialysis-dependent CKD to ESA treatment to an Hb goal of 10.5 to 11.5 g/dL or 13.0 to 15.0 g/dL with 3 years of follow-up. In this study, there was a finding of a positive

Box 4. KDIGO Guideline Recommendations for Initiation and Maintenance of ESAs

3.1: Address all correctable causes of anemia (including iron deficiency and inflammatory states) prior to initiation of ESA therapy. (*Not Graded*)
3.2: In initiating and maintaining ESA therapy, we recommend balancing the potential benefits of reducing blood transfusions and anemia-related symptoms against the risks of harm in individual patients (e.g., stroke, vascular access loss, hypertension). (*1B*)
3.3: We recommend using ESA therapy with great caution, if at all, in CKD patients with active malignancy—in particular when cure is the anticipated outcome—(*1B*), a history of stroke (*1B*), or a history of malignancy (*2C*).
3.4.1: For adult CKD ND patients with Hb concentration ≥ 10.0 g/dl (≥100 g/l), we suggest that ESA therapy not be initiated. (*2D*)
3.4.2: For adult CKD ND patients with Hb concentration <10.0 g/dl (<100 g/l) we suggest that the decision whether to initiate ESA therapy be individualized based on the rate of fall of Hb 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. (*2C*)
3.4.3: For adult CKD 5D patients, we suggest that ESA therapy be used to avoid having the Hb concentration fall below 9.0 g/dl (90 g/l) by starting ESA therapy when the hemoglobin is between 9.0–10.0 g/dl (90–100 g/l). (*2B*)
3.4.4: Individualization of therapy is reasonable as some patients may have improvements in quality of life at higher Hb concentration and ESA therapy may be started above 10.0 g/dl (100 g/l). (*Not Graded*)
3.4.5: For all pediatric CKD patients, we suggest that the selection of Hb concentration at which ESA therapy is initiated in the individual patient includes consideration of potential benefits (e.g., improvement in quality of life, school attendance/performance, and avoidance of transfusion) and potential harms. (*2D*)

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3.5.1: In general, we suggest that ESAs not be used to maintain Hb concentration above 11.5 g/dl (115 g/l) in adult patients with CKD. (*2C*)
3.5.2: Individualization of therapy will be necessary as some patients may have improvements in quality of life at Hb concentration above 11.5 g/dl (115 g/l) and will be prepared to accept the risks. (*Not Graded*)
3.6: In all adult patients, we recommend that ESAs not be used to intentionally increase the Hb concentration above 13 g/dl (130 g/l). (*1A*)
3.7: In all pediatric CKD patients receiving ESA therapy, we suggest that the selected Hb concentration be in the range of 11.0 to 12.0 g/dl (110 to 120 g/l). (*2D*)

Abbreviations: CKD, chronic kidney disease; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; KDIGO, Kidney Disease: Improving Global Outcomes; ND, nondialysis.

quality-of-life benefit. Patients randomly assigned to the higher Hb target experienced improved general health and physical function scores. However, as in the Besarab et al study, there was a non–statistically significant trend to increased risk for death in the higher Hb target group.

Singh et al studied 1,432 patients with non–dialysis-dependent CKD, treated with epoetin alfa to a target Hb concentration of 13.5 g/dL or 11.3 g/dL. Median patient exposure was 16 months. No clinical benefits were demonstrable for the higher Hb group. However, there were significant safety signals, including increased risk for cardiovascular events in a composite end point in the higher Hb group. The adverse result was driven by increased risk for death and increased risk for hospitalizations for congestive heart failure.

Table 2. Suggested Starting Dose for ESAs

	Hemodialysis	NDD-CKD
Epoetin alfa	50-100 U/kg, 3×/wk	50-100 U/kg every 1-2 wk
Darbepoetin alfa	0.45 μg/kg every wk	0.45 μg/kg every 2- 4 wk
Methoxy polyethylene glycol-epoetin beta	0.6 μg/kg, every 2 wk	0.6 μg/kg every 2-4 wk

Note: Epoetin alfa, US trademarks, Epogen, Procrit; darbepoetin alfa, US trademark, Aranesp; and methoxy polyethylene glycol-epoetin beta, US trademark, Mircera.
Abbreviations: CKD, chronic kidney disease; ESA, erythropoiesis-stimulating agent; NDD, non–dialysis-dependent.

Pfeffer et al reported on a study of 4,038 patients with type 2 diabetes mellitus and non–dialysis-dependent CKD. Participants were randomly assigned to darbepoetin alfa treatment to an Hb target of 13 g/dL (actual achieved median Hb was 12.5 g/dL) or placebo, with rescue darbepoetin treatment only as required. With a mean of 29.1 months of follow-up, no substantial benefit of the treated group was found for any end point. The major safety risk identified was increased risk for stroke in the darbepoetin-treated group (hazard ratio, 1.92; 95% confidence interval, 1.38-2.68). In addition, as in many of these studies, there were increases in thromboembolic complications.

The reasons for increased risk with ESA treatment to normal Hb targets are unclear. Greater blood viscosity at higher Hb concentrations may contribute by increasing vascular endothelial wall stress. In contrast, it may be that risk is not due to the higher achieved Hb concentration itself, but instead to the very high ESAs doses required to normalize Hb concentrations. It is possible that these supraphysiologic erythropoietin concentrations might have detrimental off-target effects. Along these lines, analyses of the higher Hb target studies have consistently had an intriguing finding. Although there was increased risk in the higher Hb target groups, counterintuitively, patients who achieved higher Hb concentrations in the studies had better outcomes. It was higher ESA doses that correlated most strongly with adverse outcomes. This suggests, but does not prove, that high ESA doses may be toxic.

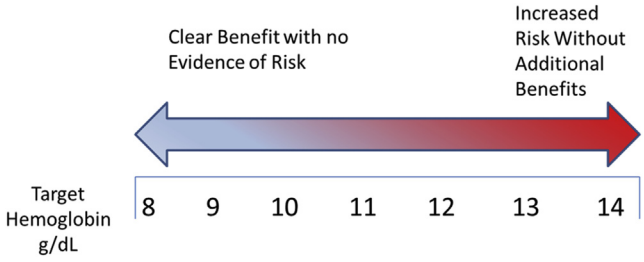

Figure 3. Target hemoglobin (Hb) concentration during erythropoiesis-stimulating agent treatment is an important determinant of the balance of benefits and risks. At lower targets, there are clear benefits with little evidence of risk; at higher Hb targets there is increased risk with no accompanying benefit.

The FDA recommends using the lowest ESA dose required to achieve therapeutic benefit.

Taken together, all acquired knowledge on ESA treatment in patients with CKD indicates clear benefits for patients with baseline Hb concentrations < 10 g/dL and moderate treatment goals. In contrast, risks are present with extended treatment to Hb targets > 13 g/dL. It is less clear regarding the relative balance of benefit and risk in patients treated to Hb targets between 10 and 13 g/dL (Fig 3). It is probably true that as Hb concentration exceeds 11 g/dL and approaches 13 g/dL, the potential benefits of treatment diminish and risks increase. Our recommendation is to target an Hb concentration of 10 to 11.5 g/dL, seeking to provide patients with the benefits of therapy while diminishing potential risks. As in all medical treatment, clinical judgment is needed. Individualization of the Hb target may be considered based on patient characteristics. For example, if a patient is asymptomatic with an active life and ESA-treated Hb concentration is 10 g/dL, there is little reason to increase the Hb concentration further. In contrast, for a younger active patient experiencing continued fatigue with an Hb concentration of 10.5 g/dL, treatment to a higher Hb concentration may be tried.

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APPENDIX

Answer to Question 1: (b) In stage 5 CKD, anemia is common, especially among patients with diabetes. Diabetes is not the cause of the anemia. Rather, relative erythropoietin deficiency is the primary causal factor.

Answer to Question 2: (c) Hypoxia-inducible factor (HIF)-prolyl hydroxylase plays the central role in oxygen sensing. In the presence of sufficient oxygen, prolyl hydroxylases (PHDs) "tag" HIF with ubiquitin, triggering degradation. When hypoxia is present, HIF is stabilized and interacts with and promotes transcription of many genes responsible for cellular protection against hypoxia, including erythropoietin.

Answer to Question 3: (c) The patient's level of kidney function is sufficiently diminished to indicate that relative

erythropoietin deficiency is probably present. However, as part of a complete evaluation of anemia, hypercalcemia was identified. When present in CKD, hypercalcemia should always suggest the possibility of a malignancy (in CKD, patients generally have a normal or low serum calcium concentration). The triad of anemia, reduced kidney function, and hypercalcemia might place special emphasis on the possibility of multiple myeloma.

Answer to Question 4: (e) During the fairly large increase in hemoglobin concentration from 7.1 to 9.8 g/dL, large quantities of iron were transferred from the body's storage pools to the developing erythron. Iron deficiency frequently develops during the first months of recombinant human erythropoietin therapy for this reason. The best answer is to add treatment with intravenous iron.