Diabetes is one of the most common causes of chronic kidney disease (CKD). Anemia is a frequent complication of CKD. This article reviews the treatment of anemia in patients with CKD. Topics include the prevalence of anemia in this population, causes and impact of anemia in these patients, target hemoglobin goals, treatment and monitoring, and causes of hyporesponse to anemia treatment.

**In Brief**

Chronic kidney disease (CKD) is a prevalent, worldwide condition, and the number of patients affected continues to increase. In the United States, it is estimated that, by 2010, > 2 million people will be afflicted with CKD. Although the most severe form of CKD is kidney failure and the need for renal replacement therapy (hemodialysis, peritoneal dialysis, or renal transplantation), many more patients are affected by less severe forms of CKD. The National Kidney Foundation (NKF) Kidney Disease Outcomes Quality Initiative (KDOQI) defines CKD based on glomerular filtration rate (GFR) and divides the disease into five distinct stages. In Stage 1 CKD, the GFR is ≥ 90 ml/min/1.73 m². Stages 2, 3, and 4 CKD are defined by a GFR of 60–89 ml/min/1.73 m², 30–59 ml/min/1.73 m², and 15–29 ml/min/1.73 m², respectively. The final stage, Stage 5, occurs when the GFR is < 15 ml/min/1.73 m² or when patients require dialysis.

**Definition of Anemia**

Anemia, as defined by the NKF, is a hemoglobin (Hb) concentration < 12 g/dl for women and < 13.5 g/dl for men. Conversely, the European Best Practices Guidelines for the Management of Anemia in Patients with Chronic Renal Failure defines anemia according to age and sex. Anemia is defined as an Hb concentration of < 11.5 g/dl in women, < 13.5 g/dl in men ≤ 70 years of age, and < 12 g/dl in men > 70 years of age. In patients receiving dialysis, the recommended Hb target value is ≥ 11 g/dl in women and ≥ 12 g/dl for men. Regardless of the definition, anemia is a common complication associated with CKD.

**Prevalence**

Anemia occurs early in the development of kidney disease and worsens with declining kidney function. Many studies have demonstrated an association between the Hb concentration and kidney function. One of the largest, the Third National Health and Nutrition Examination Survey (NHANES III), examined more than 15,000 people in the general U.S. population between 1988 and 1994 and found an inverse relationship between GFR < 60 ml/min/1.73 m² and prevalence of anemia. Using estimated GFR, the prevalence of anemia, defined as an Hb concentration < 12 g/dl in men and < 11 g/dl in women, increased from 1% in patients with a GFR of 60 ml/min per 1.73 m² to 9% at a GFR rate of 30 ml/min/1.73 m² and to 33% for men and 67% for women at a GFR of 15 ml/min/1.73 m².

Although it is known that anemia is common in patients with CKD, the impact of diabetes on the prevalence of anemia in patients with CKD has not been well established. In a recent study, three groups of patients were compared: those with type 2 diabetes without CKD \( (n = 75) \), those with type 2 diabetes and CKD \( (n = 106) \), and those with CKD without diabetes \( (n = 100) \). The investigators found that, although anemia was most
common in patients with CKD and diabetes (70.5%), it was also present in 16% of patients with diabetes alone. In patients with CKD Stages 4 and 5, the prevalence of anemia was significantly higher in those with diabetes compared with those who did not have diabetes. The authors noted that a higher awareness of the prevalence of anemia in patients with CKD and diabetes will allow earlier diagnosis and treatment.7

Causes of Anemia
Diabetes is one of the most common causes of CKD. Although patients with diabetes are regularly monitored for a variety of complications, such as neuropathy, nephropathy, and retinopathy, Hb concentrations frequently are not routinely assessed. Interestingly, reductions in Hb often occur before the onset of overt diabetic nephropathy.

This reduction in Hb occurs for a variety of reasons. Approximately 90% of the hormone erythropoietin is produced by the kidneys. Under normal physiological conditions, hypoxia in the kidney leads to an increase in the production of the hormone, which subsequently stimulates erythropoiesis.5 The kidney, in turn, senses increased oxygenation because of the formation of the new erythrocytes and decreases erythropoietin production. However, tubulointerstitial damage associated with diabetes occurs early in the course of diabetes, even before a reduction in GFR or albuminuria is noted.9 As functional renal tissue declines in patients with CKD, the body is unable to produce adequate amounts of erythropoietin in response to hypoxia in the kidney.6 Another factor commonly seen in patients with diabetes is the use of medications that may adversely affect Hb production. These include metformin, fibrate, thiazolidinediones, and angiotensin-converting enzyme inhibitors. Finally, systemic inflammation associated with microvascular disease in patients with diabetes leads to the production of inflammatory mediators, such as interleukins and tissue necrosis factor. These mediators blunt the effect of erythropoietin on the bone marrow, where erythroid precursors are stimulated.7

Other factors, although not specific to patients with diabetes, further exacerbate anemia in patients with CKD. These include platelet dysfunction leading to an increased risk of gastrointestinal bleeding, shortened erythrocyte survival time (30–60% of the normal 120 days), and hemolysis secondary to uremic toxin accumulation. In patients receiving dialysis and especially those on hemodialysis, chronic blood loss resulting from frequent phlebotomy for laboratory studies and loss of blood in the dialysis tubing and dialyzer after each hemodialysis treatment may also contribute to declining Hb values. Finally, malnutrition and deficiencies of iron, folate, and vitamin B12 have been found to cause a reduction in Hb concentrations.10

Impact of Anemia
The impact of anemia on patients with CKD is profound. In addition to the well-known symptoms of fatigue, dizziness, and shortness of breath, anemia has been associated with more severe adverse outcomes, such as cardiovascular complications including left ventricular hypertrophy and congestive heart failure. In patients with diabetes, anemia has been associated with a decline in kidney function, which often occurs in patients with diabetes. Hypoxia caused by anemia stimulates the renin-angiotensin-aldosterone system and contributes to renal vasoconstriction. These factors further exacerbate proteinuria by increasing protein in the renal tubules in patients with diabetes.9 Of note, in patients with type 2 diabetes, anemia has been shown to be an independent risk factor associated with the loss of kidney function.11 In patients with diabetes, anemia can also contribute to the severity of cardiovascular disease and independently increase the risk of retinopathy. Anemia is also thought to hasten the progression of diabetic neuropathy.11 Other general complications associated with anemia include reduced cognitive function and mental acuity, impaired quality of life, and the need for blood transfusions.12-15

Correction of anemia has been shown to improve cardiac function possibly by reducing exercise-induced myocardial ischemia.12 Treatment of anemia associated with CKD has also been shown to result in improvements in exercise capacity; physical performance features such as endurance; energy; and physical mobility.13 Patient satisfaction increases when anemia is corrected, as evidenced by higher quality-of-life scores, improved sexual function, better cognition, less depression, and better socialization.14 In non-dialysis-dependent CKD patients, stabilization of renal function has been associated with treatment of the anemia of CKD.12 Finally, treatment of anemia has been shown to reduce hospitalization and mortality rates.15

As a result of the potentially severe consequences of anemia in CKD, early recognition and management of anemia are imperative. Consequently, monitoring Hb and detecting anemia in patients with diabetes is essential.

Target Hb Goals
The decision to initiate treatment is based on the potential benefits (e.g., improvements in quality of life and symptoms and avoidance of the need for blood transfusions) and risks.9 However, the Hb value at which treatment of anemia should be initiated and the target Hb concentration is not known. The 2006 NKF KDOQI-recommended target Hb concentration is ≥11–12 g/dl, with recommendations against routinely maintaining Hb concentrations of ≥13 g/dl in patients with CKD.4 After publication of the Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) study and Cardiovascular Risk Reduction by Early Anemia Treatment With Epoetin Beta (CREATE) trials, the upper limit of the Hb target range was questioned.16,17

In the CHOIR study, Singh et al.18 randomized 1,432 patients with non–dialysis-dependent CKD to once-weekly epoetin to achieve a target Hb concentration of 13.5 g/dl versus a target Hb concentration of 11.3 g/dl. The cause of CKD was diabetes in 46.8 and 50.8% of patients randomized to the higher Hb range and the lower Hb range groups, respectively. The investigators hypothesized that patients with a higher Hb concentration would have a lower risk of complications from cardiovascular causes and death compared with those who had a lower Hb value. The authors found that patients randomized to the higher Hb concentration had an increased risk of death, myocardial infarction, hospitalization for congestive heart failure, and stroke.16 However, this study had a number of limitations, one of which was a high drop-out rate.18 Only about half
of the 1,400 randomized patients completed the trial.

More patients randomized to the higher Hb target had hypertension and had a history of coronary artery bypass surgery. In addition, compared with other studies of epoetin, patients in the CHOIR study required much higher doses of erythropoietin, with a median dose of 11,000 units, almost three times the median dose in other studies. Despite the high doses, patients in the higher Hb group did not achieve the target 13.5 g/dl Hb; the median Hb in this group was 12.5 g/dl. Although there was a statistical significance in the composite end point, there was no difference in mortality between the treatment groups during the study and during the 90-day follow-up period. Quality of life, as assessed by the Linear analogue Self-Assessment, the Kidney Disease Questionnaire (KDQ), and the Medical Outcomes Study 36-item Short-Form Health Survey (SF-36), did not differ between the two treatment groups, a finding that contradicts many other trials. Finally, this trial was prematurely terminated by the data and safety monitoring board because of an inability to demonstrate a benefit (futility) and because of the suggestion of harm with the higher Hb target, which was not achieved.18

Similarly, in the CREATE trial, 603 patients with anemia in Europe, Asia, and Mexico with Stage 4 CKD were randomly assigned to a target Hb range of either the normal range (13–15 g/dl) or the subnormal range (10.5–11.5 g/dl).17 Approximately one-fourth of patients in each group reported a prior diagnosis of diabetes. Patients were treated with subcutaneous epoetin beta, an erythropoiesis stimulating agent (ESA) not currently available in the United States, when the Hb concentration was < 10.5 g/dl. The primary outcome was a composite of 8 cardiovascular events. In the 3-year follow-up period, the investigators found no significant difference in cardiovascular event rates or in all-cause mortality between the treatment groups, but patients in the higher Hb group had higher quality-of-life scores. The mean time to dialysis was significantly shorter among patients with the normal Hb target range than among those with a lower Hb target range, but there was no difference in the rate of decline in GFR or actual GFR at the time of dialysis. Therefore, the finding of the increased need for dialysis in the higher Hb range may be an artifact.18 The authors concluded that in patients with non–dialysis-dependent CKD, correction of anemia to a target Hb range of 13–15 g/dl does not reduce the risk of cardiovascular events.17

Neither CHOIR nor CREATE provided information specific to the diabetic population. The Trial to Reduce Cardiovascular Events With Aranesp Therapy (TREAT) is an ongoing trial designed to evaluate treatment of anemia with darbepoetin alfa on mortality and cardiovascular disease (myocardial infarction, acute myocardial ischemia, congestive heart failure, stroke) in patients with CKD and type 2 diabetes. The trial investigators plan to enroll ~ 4,000 patients, who will be randomized to either darbepoetin alfa to achieve a target Hb of 13 g/dl or a control group. In the control group, placebo will be administered when the Hb is ≥ 9 g/dl and darbepoetin alfa “rescue” will start when the Hb falls to < 9 g/dl.19

Until the results of the TREAT trial are published, general recommendations for the target Hb must be used in patients with diabetes. As a result of CREATE and CHOIR, in March 2007, the U.S. Food and Drug Administration added a black-box warning to the labeling of epoetin alfa and darbepoetin alfa to highlight that the use of ESAs may increase the risk of serious cardiovascular events and death when dosed to achieve a target Hb > 12 g/dl.20–22 The warning was updated in November 2007 and states that, “ESAs should be used to maintain a hemoglobin level between 10 g/dl to 12 g/dl. Maintaining higher hemoglobin levels in patients with chronic kidney failure increases the risk for death and for serious cardiovascular reactions such as stroke, heart attack, or heart failure.” Similarly, the 2007 NKF update of the Hb target recommendation states that, although the lower limit of the target Hb range remains 11 g/dl, the target range is 11–12 g/dl, and patients who are receiving an ESA should maintain an Hb target that is ≤ 13 g/dl.21

**Treatment**

Optimal treatment of anemia due to CKD requires appropriate diagnosis, ESA and iron therapy, and close monitoring of response. The treatment is summarized in Figure 1.

**ESA therapy**

ESAs and iron are the mainstays of treatment for anemia associated with CKD. ESAs are used to stimulate erythropoiesis by either directly or indirectly acting on the erythropoietin receptor. Two ESAs are available in the United States and Canada: epoetin alfa and darbepoetin alfa. These ESAs, along with epoetin beta, are available in Europe. Recommended dosing guidelines of epoetin alfa and darbepoetin alfa are summarized in Table 1.

In patients with CKD not yet on dialytic therapy or those receiving peritoneal dialysis, epoetin alfa is typically administered once weekly or once every other week, usually by the subcutaneous route so that the dose can be self-administered at home. In patients receiving hemodialysis, epoetin is typically administered three times weekly by the intravenous route at each hemodialysis session.

Darbepoetin alfa has a significantly longer serum half-life than epoetin alfa, allowing less frequent administration while maintaining the same erythropoietic response. Darbepoetin alfa is typically initiated once weekly, but in patients not yet on dialysis or those receiving peritoneal dialysis, less frequent dosing, up to once every 4 weeks, has been used. Darbepoetin alfa is equally effective whether given by the subcutaneous or intravenous route.

For all ESAs, the intravenous route of administration is preferred in patients receiving hemodialysis because of the small increased risk for pure red cell aplasia associated with subcutaneous versus intravenous administration of epoetin alfa in patients receiving hemodialysis.3

After initiation of ESA treatment, Hb concentrations should be monitored weekly until the Hb is stable and then at least monthly thereafter. ESA dose adjustments are made based on Hb concentration, target Hb range, observed rate of increase in Hb, and clinical parameters of the patient. ESA doses are generally increased or decreased by 25% no more frequently than once a month. An exception to this rule is when the Hb is increasing and approaching 12 g/dl or when the Hb concentration...
Hb testing in all patients with CKD at least annually

Hb < 13.5 g/dl, adult males, or Hb < 12 g/dl, adult females

Diagnosis of anemia

- CBC + RBC indexes to assess anemia severity, adequacy of nutrients such as vitamin B₁₂, folate, iron
- Absolute reticulocyte count (corrected for Hb value) to assess erythropoietic activity

Normochromic, normocytic CKD

Start/adjust ESA based on Hb

ESA monitoring
Monitor Hb weekly after initiating ESA until stable and then at least monthly

Adjust ESA no more frequently than every 4 weeks, unless clinically indicated (unstable Hb, bleeding, surgery, hospitalization)

Iron monitoring
Monitor monthly during initial ESA therapy, then at least every 3 months during stable ESA therapy. Monitor more frequently following blood loss, surgery, hospitalization, or after a course of IV iron

In the past, when the Hb concentration increased too rapidly or exceeded the upper limit of the target Hb range, ESA doses were withheld. Therapy with the ESA was restarted at a later time, when the Hb declined to within the defined target range, usually at a reduced dose or maintained at the same dose with a reduced frequency if the ESA was being administered by the subcutaneous route. However, the practice of holding doses of ESAs can lead to abrupt reductions in Hb concentration, often to concentrations below the target Hb range, a situation known as “cycling.” To prevent the cycling of Hb levels encountered when ESA doses are withheld, current practice is to decrease ESA therapy either by reducing the dose or by reducing the frequency of administration.

Assessment of iron stores
Without adequate iron stores, ESAs will not be effective. In patients who do not have CKD, yearly iron loss is ~500 mg. Conversely, in patients with CKD on hemodialysis, annual iron loss can amount to 2–4 g or more. Patients with CKD may become iron deficient for a number of reasons.

CBC, complete blood count; CHr, reticulocyte hemoglobin; CKD, chronic kidney disease; ESA, erythropoiesis stimulating agent; Hb, hemoglobin; HD, hemodialysis; IV, intravenous; PD, peritoneal dialysis; PO, by mouth; RBC, red blood cell; TSAT, transferrin saturation.

### Table 1. Recommended Dosing Guidelines of Currently Available ESAs and Iron Products in the United States

<table>
<thead>
<tr>
<th>Generic Name(s)</th>
<th>Brand Name(s)</th>
<th>Route of Administration</th>
<th>Initial Dose</th>
<th>Common Adverse Effects</th>
<th>Comments</th>
</tr>
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<tbody>
<tr>
<td><strong>ESAs</strong></td>
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</tr>
<tr>
<td>Darbepoetin alfa</td>
<td>Aranesp</td>
<td>IV/SC</td>
<td>0.45 µg/kg once weekly</td>
<td>Minimal</td>
<td>IV recommended in patients receiving hemodialysis</td>
</tr>
<tr>
<td>Epoetin alfa</td>
<td>Epogen, Procrit</td>
<td>IV/SC</td>
<td>50–100 units/kg 3 times/week</td>
<td>Minimal</td>
<td>IV recommended in patients receiving hemodialysis</td>
</tr>
<tr>
<td><strong>Iron Products</strong></td>
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<td></td>
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<tr>
<td>Ferrous sulfate, ferric gluconate, polysaccharide iron complex, other</td>
<td>Various</td>
<td>PO</td>
<td>200 mg elemental iron/day</td>
<td>Constipation, abdominal pain, dark stools, drug interactions</td>
<td>Can be used in patients with CKD not yet on dialysis or those receiving peritoneal dialysis; Oral iron typically not effective to replete iron in patients receiving hemodialysis</td>
</tr>
<tr>
<td>Sodium ferric gluconate</td>
<td>Ferrlecit</td>
<td>IV</td>
<td>125 mg IV for 8 consecutive hemodialysis sessions, or 125–250 mg IV for 3–4 doses in peritoneal dialysis or in those not yet receiving dialysis</td>
<td>Dizziness, dyspnea, cramps, pruritus, nausea, hypotension</td>
<td>Test dose not required; Allergic reactions uncommon</td>
</tr>
<tr>
<td>Iron dextran</td>
<td>Infed, Dexferrum</td>
<td>IV/IM</td>
<td>100 mg IV for 10 consecutive hemodialysis sessions. In peritoneal dialysis, total dose infusions up to 1,000–1,500 mg doses × 1 have been used</td>
<td>Flushing, headache, dizziness, cramps, hypotension, tingling of extremities, nausea, shivering, dizziness</td>
<td>Use has declined significantly due to potentially fatal allergic reactions; Requires test dose</td>
</tr>
<tr>
<td>Iron sucrose</td>
<td>Venofer</td>
<td>IV</td>
<td>100 mg IV for 10 consecutive hemodialysis sessions, or 200–500 mg IV in peritoneal dialysis or in those not yet receiving dialysis</td>
<td>Dizziness, dyspnea, cramps, pruritus, nausea, hypotension</td>
<td>Test dose not required; Allergic reactions uncommon</td>
</tr>
</tbody>
</table>

IM, intramuscular; IV, intravenous; PO, by mouth; SC, subcutaneous.

In addition to physiological blood loss, patients with CKD often exhibit increased erythropoiesis and iron utilization from occult gastrointestinal blood loss resulting from platelet dysfunction that occurs with uremia. Patients on dialysis, especially those receiving hemodialysis, lose blood and, therefore, iron consequent to frequent phlebotomies for laboratory testing, vascular access manipulations and surgery, bleeding from puncture sites after dialysis, or blood clotting in the dialyzer or tubing. Thus, periodic assessment of serum iron parameters is necessary.3,10

There is no ideal test for monitoring iron storage. Most commonly, iron status is evaluated by serum ferritin and transferrin saturation (TSAT). However, ferritin is an acute-phase reactant and can be elevated for reasons other than sufficient or excessive iron stores. Examples of conditions in which serum ferritin concentrations are elevated despite iron deficiency include infection and inflammation. Similarly, transferrin, and therefore transferrin saturation, are altered in states of hypoalbuminemia and chronic disease, resulting in false TSAT values. However, because more specific and sensitive tests for the assessment of iron, such as content of Hb in reticulocytes (CHr), are not readily available, most clinicians will assess serum ferritin and TSAT. Absolute iron deficiency is defined as a serum ferritin concentration...
< 100 ng/ml in non-dialysis-dependent CKD and in patients treated by peritoneal dialysis and a serum ferritin concentration of < 200 ng/ml in hemodialysis patients. For all patients with CKD regardless of whether they are receiving dialysis, TSAT concentrations < 20% indicate iron deficiency. A number of newer tests for the evaluation of iron have been studied, but to date, the test that appears most promising is CHr measurement. This is a direct measure of iron in the reticulocyte and may be a better indicator of iron deficiency in patients with CKD. For the first time in the most recently updated NKF KDOQI guidelines, there is a recommended CHr target. In patients on hemodialysis, the KDOQI guidelines recommend a target CHr > 29 pg/cell. In trials comparing the use of reticulocyte Hb to transferrin saturation in patients on hemodialysis, patients in whom iron therapy was monitored using reticulocyte Hb targets had a reduction in intravenous iron usage and lower overall cost of anemia treatment. More recently, in the Dialysis Patients’ Response to IV Iron with Elevated Ferritin trial, a CHr of 32 pg/cell demonstrated a similar cost-efficiency outcome by aggressive yet balanced iron management.

Iron therapy

The optimal iron regimen in patients with CKD is unknown. In patients with CKD who are not receiving dialysis or those on peritoneal dialysis, iron can be given orally or intravenously. Many clinicians initiate oral iron therapy and only consider the intravenous route in patients who become intolerant or iron deficient while receiving oral therapy. Parenteral iron administration in patients with CKD not yet receiving dialysis is cumbersome and requires placement of intravenous access and multiple office visits to administer the necessary doses.

Three intravenous iron products are commercially available in the United States: iron dextran, sodium ferric gluconate, and iron sucrose. The recommended dosing guidelines of these products are summarized in Table 1. Because of concerns about life-threatening anaphylactoid reactions to iron dextran, many practitioners no longer use it; however, there are isolated instances where iron dextran is routinely used. Adverse effects of intravenous iron can be severe and include hypotension, chills, back pain, nausea, dyspnea, wheezing, stridor, chest pain, facial flushing, rash, and cutaneous symptoms of porphyria. However, in some cases, the adverse effects of iron are unrecognized because of the nonspecific nature of the reactions and the overlap between iron-related adverse effects and dialysis-related adverse effects, such as dizziness, dyspnea, cramps, pruritus, nausea, constipation, diarrhea, and hypotension. In non-dialysis-dependent CKD or peritoneal dialysis, larger single doses of iron sucrose or sodium ferric gluconate have been used (e.g., iron sucrose, 300 mg, or sodium ferric gluconate, 250–375 mg infused during 1 hour). In contrast, intravenous iron administration is preferred in patients receiving hemodialysis because it is unlikely that these patients will absorb a sufficient amount of orally administered iron to replace ongoing losses that are associated with hemodialysis. In these patients, there are two methods to administer iron: as a loading dose for replenishment of depleted stores or as a maintenance dose to compensate for ongoing iron losses. In iron loading, iron is given periodically to replenish iron stores (e.g., 1,000 mg given during 8 or 10 consecutive dialysis sessions). After repletion of iron stores, small intravenous maintenance doses (e.g., 50–125 mg) of iron weekly, every other week, or monthly can be administered to maintain iron stores at acceptable concentrations.

Iron studies should be monitored monthly during initial ESA therapy because of the need for adequate

<table>
<thead>
<tr>
<th>Table 2. Causes of Hyporesponse to ESA Therapy in Patients With CKD</th>
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<tbody>
<tr>
<td>Acute blood loss (e.g., surgery, vascular access interventions, gastrointestinal bleed)</td>
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<tr>
<td>Acute infection/inflammation</td>
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<tr>
<td>Aluminum toxicity</td>
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<tr>
<td>Cancer/malignancy</td>
</tr>
<tr>
<td>Chronic blood loss (e.g., frequent clotting of dialyzer, excessive post-dialysis bleeding, frequent phlebotomy)</td>
</tr>
<tr>
<td>Chronic conditions (e.g., HIV, sickle cell anemia, thalassemia, pregnancy)</td>
</tr>
<tr>
<td>Chronic infection/inflammation (e.g., systemic lupus erythematosus, failed kidney transplant, catheter-associated inflammation)</td>
</tr>
<tr>
<td>Diabetes</td>
</tr>
<tr>
<td>Hyperparathyroidism: longstanding</td>
</tr>
<tr>
<td>Iron deficiency</td>
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<tr>
<td>Medications</td>
</tr>
<tr>
<td>Nonadherence to ESA or iron therapy</td>
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<tr>
<td>Pure red cell aplasia: production of antibodies that neutralize ESA and endogenous erythropoietin</td>
</tr>
<tr>
<td>Uremia/suboptimal dialysis</td>
</tr>
<tr>
<td>Vitamin and/or mineral deficiency (folic acid, vitamin B12, iron)</td>
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<tr>
<td>HIV, human immunodeficiency virus.</td>
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iron and the rapid consumption of iron during erythropoiesis. The 2006 KDOQI anemia treatment guidelines state: “There is insufficient evidence to recommend routine administration of intravenous iron if ferritin level is greater than 500 ng/ml.” However, others consider the upper safe limit of ferritin to be 800–1,200 ng/ml.24 The generally accepted upper limit for TSAT is 50%.3 Once the dose of ESA and Hb are stable, iron can be monitored less frequently, but at least every 3 months. More frequent monitoring of iron may be necessary after significant blood loss or surgery, during hospitalization, or to monitor the response to a course of intravenous iron.3,4,10,27

Hyporesponsiveness to ESA therapy
Hyporesponsiveness to ESA therapy is a common yet often frustrating problem encountered in patients with CKD. Hyporesponsiveness to ESAs is defined as a condition in which there is a significant increase in the ESA dose requirement to maintain an Hb level within a specified Hb range, a significant decrease in Hb concentration at a constant ESA dose, or failure to achieve an Hb concentration of ≥11 g/dl despite an ESA dose equivalent to epoetin β > 500 units/kg/week. There are a number of causes of hyporesponsiveness to ESA therapy (Table 2).

Treatment recommendations suggest that all patients with anemia and CKD should undergo evaluation for specific causes of hyporesponsiveness whenever the Hb concentration is inappropriately low for the ESA dose administered. In some patients, there may be more than one cause of hyporesponsiveness. Although not all causes of hyporesponsiveness are correctable, easily correctable causes should be addressed as soon as possible. Other causes, such as secondary hyperparathyroidism or hematological malignancies, may require longer periods of time to correct.3,4,10,27 Chronic medical conditions, such as systemic lupus erythematosus or sickle cell anemia, may not be correctable.10,27

Of interest, a recent study evaluating predictors of hyporesponsiveness to ESAs in patients not on dialysis found that diabetes is one factor that is associated with the need for higher ESA doses.26 The authors pointed out that patients with diabetes and anemia manifest excessively low endogenous erythropoietin concentrations and that this may be responsible for the need for higher doses of ESA in this patient population.

Summary
CKD is a prevalent, worldwide condition, and the number of patients affected continues to increase. Diabetes is one of the most common causes of kidney disease. Anemia occurs early in development of kidney disease and worsens as kidney function deteriorates. Anemia has been associated with substantial morbidity and mortality. However, with appropriate therapy with ESAs and iron, anemia can be effectively treated, thereby improving the quality of life in patients with CKD and anemia.

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Ferric gluconate is highly efficacious in anemic hemodialysis patients with high serum ferritin and low transferrin saturation: results of the dialysis patients’ response to IV iron with elevated ferritin (DRIVE) study. *J Am Soc Nephrol* 18:975–984, 2007


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