Anemia of Chronic Renal Failure

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Cover Illustration by May S. Cheney
Anemia of Chronic Renal Failure

Anemia substantially influences the quality of life, morbidity, and survival of patients with advanced renal failure. The modern history of anemia and chronic renal failure (CRF) began in 1957 when Jacobson et al demonstrated that erythropoietin, the hormone that regulates erythropoiesis, is produced by the kidneys. Since that discovery, human urinary erythropoietin has been purified, the gene for human erythropoietin has been isolated and cloned, and recombinant human erythropoietin (r-HuEPO) has been synthesized and approved for treatment. r-HuEPO is now used worldwide in patients with CRF and end-stage renal disease (ESRD). This manual reviews the nature and pathophysiology of the anemia that accompanies CRF, emphasizing its treatment with r-HuEPO and supplemental iron.

### Pathophysiology and Clinical Manifestations

#### Case Patient Presentation

During a follow-up visit to her nephrologist, a 62-year-old woman reports worsening of her previously stable angina pectoris over the previous 2 months and increasing symptoms of fatigue, anorexia, and dyspnea on exertion.

**History**

The patient has a history significant for long-standing type 2 diabetes mellitus and chronic renal insufficiency. In addition, she has had hypertension for many years, which has been treated with furosemide, tenormin, and captopril. The patient was hospitalized 2 years ago with congestive heart failure and is known to have diabetic retinopathy.

**Physical Examination**

Physical examination reveals a pale-appearing woman with a blood pressure of 130/70 mm Hg and a pulse of 100 bpm. Ear, nose, and throat examination is negative. Lung examination reveals basilar crackles, and cardiac examination reveals a normal S1 and S2, as well as an S3. Abdominal examination is negative. A test for fecal occult blood is negative. Neurologic examination is unremarkable, and there is no asterixis.

**Laboratory Testing**

Laboratory studies reveal the following: blood glucose, 210 mg/dL; hematocrit (Hct), 24%; hemoglobin (Hb), 7.8 mg/dL; blood urea nitrogen (BUN), 70 mg/dL; and serum creatinine, 6.0 mg/dL. The BUN and serum creatinine levels are unchanged from values obtained 4 months ago. Electrolytes and liver function tests are unremarkable. The mean corpuscular volume (MCV) is 90 fL, with a mean corpuscular Hb concentration (MCHC) of 34 g/dL. Urinalysis reveals 3+ protein with a few hyaline and granular casts. A 24-hour urine collection demonstrates 6.2 g protein and a creatinine clearance of 14 mL/min. Echocardiography reveals well-preserved systolic function with left ventricular hypertrophy (LVH).

- What are the most important factors contributing to this patient’s anemia?

### Pathophysiology of the Anemia of CRF

The kidneys produce 85% to 90% of the body’s erythropoietin, with most of the remainder produced by the liver. Renal production of erythropoietin decreases as kidney function declines. In most patients, anemia develops after the glomerular filtration rate decreases below 30 to 45 mL/min, but in patients with polycystic kidney disease, erythropoiesis tends to be better preserved than in patients with other causes of ESRD.

Erythropoietin production is stimulated by the reduced oxygen carrying capacity of blood delivered to pericapillary, fibroblast-like interstitial cells in the kidneys. Hypoxia-inducible factor, a protein produced in
response to hypoxemia, binds to a hypoxia-responsive enhancer located downstream from the erythropoietin gene on chromosome 7 and increases gene transcription. This gene encodes a 193–amino acid polypeptide, which is partially cleaved during secretion. The resulting human erythropoietin is a 165–amino acid glycoprotein, with 4 carbohydrate moieties that are essential for its physiologic activity. Erythropoietin stimulates differentiation of erythroid progenitors and increases Hb synthesis via a transmembrane protein receptor present on the burst-forming and colony-forming units.5,6

Erythropoietin deficiency is recognized as the principal cause of anemia in patients with CRF and ESRD. Iron deficiency is an important contributing factor in the anemia of CRF, especially in ESRD patients on hemodialysis. The relative importance of other factors that may contribute to the pathogenesis of anemia in CRF has been a matter of much speculation.3,6 Mild intravascular hemolysis may occur in some individuals with CRF. The cause of the shortened erythrocyte life span in patients with CRF is unknown; however, an unidentified circulating toxin may play a role, based on the fact that when erythrocytes are transfused from patients with renal failure into normal individuals, their life span is normalized. Erythropoietin deficiency itself may reduce erythrocyte life span, perhaps as a result of selective hemolysis of young erythrocytes (neocytolysis) in the relative absence of erythropoietin.7 Although early studies suggested that dialysis did not improve erythrocyte survival, recent evidence suggests that hemolysis is not likely a significant contributing factor in patients who are well dialyzed and receiving r-HuEPO.6

The presence of circulating inhibitors of erythropoiesis such as spermine, parathyroid hormone, and so-called “middle molecules” has long been postulated in patients with CRF, but they are most likely not an important factor in most patients. Cytokines contribute to r-HuEPO resistance in patients with infectious or inflammatory conditions and may also have a role in inhibiting normal erythropoiesis and contributing to the development of anemia in patients with CRF.

• What is the role of anemia in the symptoms and morbidity associated with advanced renal failure?

CLINICAL MANIFESTATIONS OF THE ANEMIA OF CRF

Many symptoms previously attributed to uremia appear to result in part from coexisting anemia or can be improved with treatment of anemia. Even partial correction of anemia with r-HuEPO improves patients’ overall sense of well-being and satisfaction with their health; physical symptoms such as weakness, fatigue, somnolence, and anorexia; and scores on quality of life assessments. Correction of anemia also may lead to improvements in cognitive and neuropsychiatric disturbances, angina pectoris, exercise intolerance, dyspnea, sexual dysfunction, loss of libido, pruritus, and cold intolerance attributed to uremia. In addition, correction of anemia improves platelet function and decreases uremic bleeding tendencies.

LVH, a major risk factor for cardiac morbidity and mortality in patients with ESRD, increases in prevalence as renal function declines and is present in as many as 75% of patients beginning dialysis.8 Cardiovascular responses to the chronic progressive anemia of CRF that may contribute to development of LVH include arterial vasodilation (with reduced vascular resistance and afterload) and increased heart rate, stroke volume, and cardiac index. Both left ventricular mass and end diastolic volume have been shown to correlate inversely with changes in Hb levels. However, even partial correction of anemia can ameliorate these hemodynamic changes and reverse LVH to some degree.9

TESTING AND r-HuEPO TREATMENT

INITIAL MANAGEMENT OF CASE PATIENT

The patient is admitted to the hospital with a diagnosis of unstable angina. She is transfused 2 U of packed erythrocytes, but her angina persists. Cardiac catheterization is recommended. After the patient understands that dialysis will likely be required after the procedure, a cardiac catheterization is performed and reveals stenoses in the left anterior descending and circumflex coronary arteries. Two days later, percutaneous transluminal coronary angioplasty of these areas is performed. The patient experiences worsening azotemia accompanied by nausea, vomiting, and development of asterixis following the procedures. As a result, a temporary dialysis catheter and left brachiocephalic synthetic bridge graft are placed and hemodialysis (initially using the catheter) is begun. Laboratory studies 3 weeks later reveal an Hb level of 7.3 g/dL and an Hct of 20%.

• What studies should be performed to evaluate anemia in patients with advanced renal failure?
• What treatments are available and recommended for initial management of the case patient’s anemia?

RECOMMENDED DIAGNOSTIC TESTS

The anemia of CRF is normochromic and normocytic, with a low corrected reticulocyte count, burr cells on
the peripheral blood smear, and a normocellular marrow. Patients with CRF and anemia should be evaluated for causes other than renal failure, especially iron deficiency due to chronic gastrointestinal (GI) or menstrual blood losses and vitamin B12 or folate deficiency (Table 1). Measurement of erythropoietin levels and evaluation of bone marrow usually are not indicated, although the latter may be necessary in specific circumstances.

**TREATMENT WITH r-HuEPO**

Prior to the availability of r-HuEPO, treatment for the anemia of CRF and ESRD in patients without iron deficiency was limited to renal transplantation, erythrocyte transfusions, and administration of androgens. Androgens such as nandrolone decanoate and fluoxymesterone improve anemia, reduce the requirement for transfusions in dialysis patients, and 25 years ago were thought to be the most effective erythropoietic stimulants available.10 Androgens increase erythropoietin production and stimulate heme synthesis and erythroid stem cell differentiation in the marrow. Adverse effects of androgen therapy include pain and hematoma formation at the intramuscular injection site, aggravation of hypertriglyceridemia, hepatic disorders, virilization, acne, priapism, and changes in libido.

Transfusion is unquestionably effective in correcting anemia but is also associated with an increased risk of transmitting infectious agents (eg, hepatitis B and C viruses, HIV) and may further suppress erythropoietin production. Antibodies to human leukocyte antigen or other antigens may develop, a factor that is important to potential renal transplant candidates. Chronic transfusional iron overload may result in cardiac dysfunction, proximal myopathy, and hepatic dysfunction. Fortunately, treatment with r-HuEPO mobilizes storage iron for erythropoiesis and quickly eliminates or markedly reduces the need for further transfusion.

In the absence of iron deficiency or other reversible causes, anemia management in patients with renal failure is based on replacement of a deficient hormone, a therapeutic approach analogous to use of insulin in type 1 diabetes. Currently, r-HuEPO is the primary therapy for the anemia of CRF and ESRD. A dose-response relationship for intravenous (IV) administration of r-HuEPO was observed in early clinical trials in hemodialysis patients4 (Figure 1). Subsequent clinical experience has revealed tremendous variability in patient response to r-HuEPO and in maintenance dose requirements. The National Kidney Foundation Dialysis Outcomes Quality Initiative (NKF-DOQI),11 the European Renal Association/European Dialysis and Transplant Association,12 and the Canadian Society of Nephrology13 have each provided evidence-based guidelines for managing anemia in patients with CRF and ESRD. These guidelines recommend starting r-HuEPO therapy with 50 to 180 U/kg/week given in 2 or 3 divided doses, with a goal of increasing the Hb level at a rate of approximately 2 to 2.5 g/dL, or increasing Hct by approximately 6% to 8%, over 4 weeks until the desired Hb or Hct level is reached.

When r-HuEPO treatment is initiated or the dosage is modified, the Hb and Hct levels usually are monitored every 1 to 2 weeks until a stable Hb or Hct level is achieved, then every 2 to 4 weeks thereafter. If the rate of increase in Hb or Hct level is less than desired over a 2- to 4-week period, the dose can be increased by 25% to 50%. If the rate of increase in Hb or Hct level is excessive (ie, greater than approximately 8 Hct percentage points or 2.5 to 3.0 g/dL Hb over 4 weeks), the dose can be reduced by 25%. Unless the rate of increase in Hb or Hct level is particularly rapid or target Hb or Hct levels are significantly exceeded, the r-HuEPO dose should be decreased rather than held. This will help to minimize a “roller coaster” effect in which wide swings

<table>
<thead>
<tr>
<th>Table 1. Laboratory Testing for Evaluation of Anemia in Patients with Renal Failure</th>
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<tbody>
<tr>
<td><strong>All patients</strong></td>
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<tr>
<td>Hematocrit and hemoglobin</td>
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<tr>
<td>Complete blood count, including erythrocyte indices (MCV, MCHC)</td>
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<tr>
<td>Reticulocyte count</td>
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<tr>
<td>Serum iron, TIBC, TSAT, serum ferritin</td>
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<tr>
<td>Test for occult gastrointestinal blood loss</td>
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<tr>
<td>Vitamin B₁₂, folate levels</td>
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<tr>
<td><strong>Selected patients</strong></td>
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<tr>
<td>Haptoglobin, Coomb’s test</td>
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<tr>
<td>Serum and urine protein immunoelectrophoresis</td>
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<tr>
<td>Serum aluminum level</td>
</tr>
<tr>
<td>Parathyroid hormone level</td>
</tr>
<tr>
<td>C-reactive protein</td>
</tr>
<tr>
<td>HIV</td>
</tr>
<tr>
<td>Bone marrow and/or aspirate</td>
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<tr>
<td>Sickle cell test or hemoglobin electrophoresis</td>
</tr>
</tbody>
</table>

MCV = mean corpuscular volume; MCHC = mean corpuscular hemoglobin concentration; TIBC = total iron binding capacity; TSAT = percent saturation of transferrin.
in Hb or Hct levels occur in response to holding and then resuming r-HuEPO dosing.

**Route of r-HuEPO Administration**

During the initial clinical trials of r-HuEPO, the drug was administered intravenously. At that time, the extent of r-HuEPO’s effectiveness was uncertain, the dosing requirements were unknown, and pharmacokinetic and clinical studies of subcutaneously administered r-HuEPO had not been published. Subsequent studies have revealed that the bioavailability of subcutaneous r-HuEPO is only approximately 20% but that it has a substantially longer half-life than IV r-HuEPO (approximately 24 to 48 hours versus 6 to 10 hours). The dose of r-HuEPO can be reduced by a mean of at least 20% to 30% when administered subcutaneously compared with IV administration in hemodialysis patients, although the subcutaneous route is not more efficient in all patients. The increased efficacy of subcutaneous r-HuEPO administration most likely results from the longer half-life, although erythrocyte life span may also be increased with the more continuous exposure to r-HuEPO that occurs with subcutaneous administration.

For patients not yet on dialysis and those on peritoneal dialysis, subcutaneous administration is more convenient and leaves veins better preserved for possible future hemodialysis access. Although subcutaneous administration has also been recommended for hemodialysis patients, this method is less generally accepted, partly because of discomfort at the injection site. The original preparations of r-HuEPO contained a citrate buffer that appears to be responsible for pain with subcutaneous injection. However, use of small gauge needles and a newer preparation containing benzyl alcohol results in little or no discomfort with subcutaneous injections in most patients. In patients who are obese, have active skin disease, receive chronic anticoagulation treatment, or receive large doses of r-HuEPO, IV administration may be preferred. Intraperitoneal administration has limited applicability but may be preferred in children on peritoneal dialysis who do not tolerate subcutaneous injection.

In hemodialysis patients, r-HuEPO (IV or subcutaneous) is most commonly given 3 times weekly at each dialysis treatment. In peritoneal dialysis patients and patients not on dialysis, administration once or twice weekly (sometimes even less frequently) usually is effective. Novel erythropoiesis stimulating protein, a hyperglycosylated analogue of r-HuEPO, currently is undergoing early clinical trials. It has a terminal half-life after IV and subcutaneous administration of approximately 25 hours and 48 hours, respectively, and may allow less frequent dosing in hemodialysis patients compared with IV r-HuEPO.

**Target Hct and Hb Levels**

The Hct and Hb levels of dialysis patients have consistently improved over the past 10 years. However, the high cost of r-HuEPO and concern that increasing Hct and Hb levels in dialysis patients may have deleterious consequences have fueled debate regarding optimal Hct and Hb levels for CRF and ESRD patients. In the phase III multicenter clinical trial of r-HuEPO, target Hct levels ranged from 32% to 38%. Although the target Hct level for r-HuEPO-treated patients with CRF or ESRD initially approved by the United States Food and Drug Administration was only 30% to 33%, the NKF-DOQI guidelines recommend a target Hct range from 33% to 36% (Hb level of 11 to 12 g/dL). When anemia is partially corrected—to achieve Hb levels of 10 to 12 g/dL or Hct levels of 30% to 36%—physiologic indices (eg, exercise capacity) and quality of life measures improve; LVH begins to regress; and

Figure 1. Dose-response relationship between duration of recombinant human erythropoietin (r-HuEPO) treatment and increase in hematocrit in initial clinical trials. Doses of r-HuEPO are indicated; treatment was administered 3 times per week. Adapted with permission from Eschbach JW, Egrie JC, Downing MR, et al: Correction of the anemia of end-stage renal disease with recombinant human erythropoietin. Results of a combined phase I and II clinical trial. *N Engl J Med* 1987;316:73–78.
lengths of stay and rates of hospitalization, morbidity, and mortality decline (Figure 2). Data suggesting that Hct and Hb levels above this range offer additional clinical benefit have been more difficult to confirm. Improved exercise capacity and aerobic performance have been demonstrated at normal Hb levels. Normalization of Hct in hemodialysis patients increases oxygen supply to the brain and oxygen extraction by brain tissue, reverses the electroencephalographic slowing (ie, abnormality) observed at more anemic Hct levels, and is associated with improved neurophysiologic function.19,20 However, a large-scale prospective, randomized trial21 comparing target Hct levels of 30% and 42% in r-HuEPO-treated hemodialysis patients with congestive heart failure or ischemic heart disease was terminated early because investigators expressed concerns over a greater number of deaths and nonfatal myocardial infarctions in the normal Hct group. These differences did not reach statistical significance, however, and no differences were observed in various secondary endpoints (eg, angina pectoris, congestive heart failure requiring hospitalization). A higher incidence of vascular access thrombosis (both synthetic bridge grafts and native arteriovenous fistulae) was observed in the normal Hct group. Interpretation of this study, however, is complicated. Despite a trend toward a greater number of deaths and nonfatal myocardial infarctions in the normal Hct group, mortality rates in both groups declined with increasing Hct level. In addition, the lowest mortality rate was observed in normal Hct patients with the highest mean Hct values of 39% to 42%.

Results from ongoing studies of the effects of normalization of anemia in dialysis patients in Scandinavia and Canada may increase clinicians’ understanding of appropriate target Hb and Hct levels. Based on available evidence, however, the NKF-DOQI11 and European guideline recommendations12 are both reasonable. The latter advise maintaining Hb levels above 11 g/dL in most patients without diabetes mellitus or cardiovascular disease and between 11 and 12 g/dL in patients with those conditions.

**CLINICAL IMPORTANCE OF MAINTAINING ADEQUATE IRON STATUS**

**INITIATION OF r-HuEPO THERAPY IN CASE PATIENT**

The patient is started on treatment with r-HuEPO (6000 U subcutaneously at each dialysis treatment) and oral ferrous sulfate (325 mg twice daily). Two months later, the patient feels well, is free of angina, and is able to perform her usual activities without limitation. Laboratory studies reveal the following: Hb, 11.0 g/dL; reticulocyte count, 1%; serum iron, 80 µg/dL; serum ferritin, 110 ng/mL; total iron binding capacity, 290 µg/dL; and percent saturation of transferrin (TSAT), 27%. MCV and MCHC are within normal limits.

Over the next 3 months, the patient develops thrombosis of the arteriovenous bridge graft on 2 occasions. The first thrombosis is treated with mechanical thrombolysis and transluminal angioplasty, the second by surgical thrombectomy and revision of a recurrent graft outflow stenosis. Subsequent laboratory testing 2 weeks later reveals the following: Hb, 8.2 g/dL; TSAT, 13%; serum ferritin, 75 ng/mL.

- Which are the best tests for evaluating the iron status of patients with CRF or ESRD who are receiving r-HuEPO?

**EVALUATING IRON STATUS**

Iron deficiency occurs in many patients as a result of r-HuEPO-stimulated erythropoiesis and ongoing blood losses and is the most common cause of inadequate response to r-HuEPO. Therefore, monitoring a patient’s iron status is an integral component of optimal anemia management. Bone marrow biopsy with staining for marrow iron—the “gold standard” for assessing iron status—is not suitable for repetitive testing or for general use in large numbers of patients. An operational

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A definition of iron deficiency more appropriate for clinical use is the demonstration of an increase in Hb or Hct level or reduced requirement for r-HuEPO in response to parenteral infusion of iron.22

**Serum Ferritin and TSAT**

Although many blood tests are available for assessing iron status, all are imperfect. In the United States, the serum ferritin level and TSAT are most commonly measured. Iron is stored in reticuloendothelial cells of the liver, spleen, and bone marrow as ferritin, which is bound to the storage protein apoferritin. A soluble form of ferritin that is distinct from tissue ferritin and devoid of iron is present in the circulation. The serum ferritin concentration in normal individuals correlates reasonably well with iron stores. In patients with ESRD who have serum ferritin concentrations less than 100 ng/mL, iron deficiency is likely and iron supplementation should be provided. The serum ferritin concentration increases with increasing levels of storage iron, and iron supplementation should be withheld temporarily when the serum ferritin level exceeds 800 ng/mL. Serum ferritin may also respond as an acute-phase reactant in the presence of malignancy, infection, or inflammation. Therefore, an elevated serum ferritin level may not always indicate increased iron stores. Transferrin is the primary protein carrier of iron in the circulation, and the TSAT is the most commonly used measure of iron that is immediately available in the circulation for delivery to the erythroid marrow for erythrocyte production. TSAT can be calculated using the following equation:

\[
\text{TSAT} = \left( \frac{\text{plasma iron concentration}}{\text{total iron binding capacity}} \right) \times 100
\]

The reliability of the TSAT is affected by substantial laboratory and diurnal variability of the plasma iron level. Likewise, the serum transferrin level decreases with poor nutritional status and with cytokine generation in response to inflammatory conditions.

A TSAT less than 20% suggests that iron deficiency is likely, and a TSAT greater than 50% to 60% may be associated with excessive iron levels. Decreasing TSAT and ferritin levels suggest utilization of available iron. An increasing serum ferritin level, particularly in the absence of increases in Hb levels, may indicate excessive iron administration (typically accompanied by a normal or high TSAT) or the presence of occult infectious or inflammatory disease (typically accompanied by a low-normal TSAT).

Monitoring trends in these iron parameters is helpful in patient management. The TSAT and serum ferritin concentration should be measured every 1 to 3 months and maintained above 20% and 100 ng/mL, respectively, with administration of supplemental iron as necessary.

**Additional Tests for Assessing Iron Status**

Two additional tests for diagnosing iron deficiency in dialysis patients are the percentage of hypochromic erythrocytes in the circulation and the reticulocyte Hb content, both of which require specialized autoanalyzer methodologies not yet routinely available. The percentage of hypochromic erythrocytes in the circulation is predicted to increase before the MCHC changes and is recommended by the European Guidelines in preference to the TSAT because of laboratory and clinical variability of the TSAT.12 The reticulocyte Hb content has been reported to reflect iron deficiency more accurately than the Hb content of mature erythrocytes and may be superior for detecting both absolute and functional iron deficiency compared with either the TSAT or percent hypochromic erythrocytes.23,24 Neither test is routinely available in the United States, and specific recommendations regarding their use in this country have not been made.

**IRON BALANCE AND DEFICIENCY**

The average daily dietary intake of iron in North America is between 10 and 30 mg, of which approximately 5% to 10% (1 mg/day; 1.5 mg/day in menstruating women) is absorbed in the duodenum and proximal jejunum. In patients with iron deficiency, GI iron absorption of daily iron intake may exceed 30% to 50%. Medications such as proton pump inhibitors, histamine2 blockers, antacids, and phosphate binders reduce GI iron absorption.

**Functional Iron Deficiency**

The laboratory diagnosis of iron deficiency is complicated in some patients treated with r-HuEPO by the development of functional iron deficiency. In response to administration of r-HuEPO, erythropoiesis is briskly stimulated and may exceed the rate at which iron can be mobilized for ongoing erythrocyte production. A dis-equilibrium results between plentiful iron stores and inadequate iron in the circulation available for erythropoiesis.

Functional iron deficiency is associated with normal to high serum ferritin levels and a low or low-normal TSAT. Functional iron deficiency cannot be diagnosed using bone marrow biopsy because marrow iron is present. In patients with functional iron deficiency, a trial of parenteral iron may be helpful because it directly
provides iron for the transferrin iron pool. However, iron overload and infectious or inflammatory conditions that may impair mobilization of iron (reticuloendothelial blockade) and elevate the serum ferritin concentration as part of an acute phase response should be excluded.

- What are the sources of iron loss and iron requirements in patients with CRF and ESRD?

**IRON STORES AND LOSSES**

In normal individuals, approximately 2.0 to 2.5 g of elemental iron is contained in the Hb of circulating erythrocytes; 1 mL of packed erythrocytes contains approximately 1 mg of elemental iron. Iron in tissue stores is the second largest component of total body iron and amounts to approximately 1000 mg in adult men and approximately 300 mg in women of childbearing age. Another 300 to 400 mg is contained in myoglobin and other slow turnover stores. In the circulation, approximately 5 mg of iron is bound to the transport protein transferrin and serves as the source of iron for erythropoiesis.

Important sources of blood (ie, iron) loss in patients on hemodialysis include the following: occult GI bleeding, bleeding from venipuncture sites, residual blood in dialyzer and blood lines following treatment, and radiologic and surgical interventions for hemodialysis access and diagnostic laboratory testing. In hemodialysis patients, annual iron losses may amount to as much as 2 to 3 g. Patients with ESRD who are on peritoneal dialysis and those with CRF who are not on dialysis typically have smaller iron losses.

**USE OF IRON SUPPLEMENTS**

Most patients with CRF or ESRD who receive r-HuEPO require supplemental iron to treat iron deficiency, prevent the development of iron deficiency, and maintain adequate iron stores to achieve target Hb and Hct levels.

**Treatment with Oral versus Parenteral Iron**

Patients with CRF who are not on dialysis and those who receive peritoneal dialysis (and therefore are not subject to blood losses associated with hemodialysis) may be able to achieve adequate iron levels with oral iron supplements that provide 130 to 200 mg of elemental iron daily. None of the available oral iron preparations has been shown to be substantially superior to others in terms of efficacy or adverse effects, but ferrous sulfate is the least expensive. Annoying GI side effects (eg, gastric upset, constipation) and the inconvenience of having to take 2 to 3 additional pills per day limit compliance with oral iron. Fishbane et al recently observed that patients with such GI side effects experience a mean reduction in normalized protein catabolic rate of approximately 20%. Taking the pills with meals may reduce GI intolerance but may also reduce bioavailability.

Oral iron is of little or no use in most patients on hemodialysis who are treated with r-HuEPO, the vast majority of whom require parenteral iron to prevent iron deficiency and maintain target Hb and Hct levels. Oral iron has not been shown to reduce the need for IV iron in hemodialysis patients and should be discontinued when treatment with parenteral iron is undertaken.

Iron dextran, a colloidal suspension of ferric oxyhydroxide and low molecular weight dextrans, has long been the mainstay of IV iron therapy in the United States. Sodium ferric gluconate complex in sucrose (also referred to as ferric gluconate) has been used for many years in Europe and has recently been approved for use in the United States. Iron saccharate, another IV iron preparation used in Europe and elsewhere, is undergoing clinical testing in the United States.

**Dosing Regimen for Iron Supplements**

Several dosing regimens can be used to treat and prevent iron deficiency in hemodialysis patients (Table 2). The regular administration of parenteral iron (maintenance iron treatment) enhances erythropoiesis, reduces
r-HuEPO requirements, and most likely requires less cumulative iron compared with administration of iron only in response to iron deficiency. To achieve target Hb and Hct levels, IV iron supplementation often must be provided to maintain TSAT and serum ferritin levels above 20% and 100 ng/mL, respectively. Supplemental IV iron therapy should be temporarily discontinued if TSAT or serum ferritin levels exceed 50% or 800 ng/mL, respectively. Parenteral iron administration may cause transient elevations of TSAT and serum ferritin levels that are not indicative of steady state iron status, particularly when doses of 500 to 1000 mg are given. Therefore, these tests should be obtained no sooner than 7 days following administration of ≤ 100 mg iron dextran or ≤ 125 mg iron gluconate and 14 days following administration of larger doses.

Compared with hemodialysis patients, CRF patients not yet on hemodialysis and patients on peritoneal dialysis may respond more favorably to oral iron therapy, and treatment with parenteral iron is less commonly necessary in these patients. When parenteral iron therapy is necessary in the latter group of patients, however, “total dose infusion” with 500 to 1000 mg of iron dextran over several hours may be used as necessary, rather than treatment with lower, more frequent doses.

- What are the acute and chronic risks of parenteral iron therapy in patients with CRF and ESRD?

RISKS ASSOCIATED WITH PARENTERAL IRON THERAPY

Acute Reactions

Non-dose-related acute reactions to IV iron dextran and iron gluconate include allergic or anaphylactoid reactions with dyspnea, wheezing, pruritus, and hypotension as well as nausea, headache, chest pain, flushing, and cardiac arrest. Some of these symptoms may also develop after rapid administration of an iron dose, as a direct result of iron toxicity on a nonallergic basis. In a recent multicenter study, anaphylactoid reactions that result presumably from the presence of preformed antibodies to dextran were observed in 1.7% of dialysis patients treated with iron dextran. In addition, myalgias, arthralgias, fever, and lymphadenopathy may occur within days of iron dextran administration, particularly with larger doses of 500 to 1000 mg. Allergic and toxic reactions to ferric gluconate appear to be less common compared with reactions to iron dextran; ferric gluconate has been administered safely to patients with prior iron dextran–related anaphylactoid reactions.

Administration of a one-time 25-mg test dose is recommended prior to administration of a full therapeutic dose of any parenteral iron preparation. The patient should be monitored closely for approximately 1 hour before the full dose is given. Many acute reactions, however, occur even before the full 25-mg test dose is given. In addition, Fishbane et al observed that 60% of anaphylactoid reactions did not occur with the first dose. Therefore, careful patient monitoring is important during any IV iron administration, and trained staff and proper resuscitative medications should be available.

Concerns with Long-Term Use

The clinical efficacy of r-HuEPO in CRF and ESRD patients has created a need for repetitive administration of parenteral iron to a large number of patients and has raised concern about potential long-term toxicities. Because free iron is required for growth of many microorganisms, parenteral iron may increase the risk of infectious complications in these patients. Studies conducted before r-HuEPO was available for clinical use suggest that hemodialysis patients with transfusion-related iron overload are at increased risk for bacterial infections and bacteremia. In addition, high levels of storage iron in dialysis patients with functional iron deficiency may impair neutrophil function, although the clinical significance of this effect is unclear. Recent preliminary data suggest an association among certain patterns of parenteral iron administration, infection-related morbidity and mortality, and all-cause mortality in dialysis patients.

However, in a recent prospective study, Hoen and colleagues found neither parenteral iron administration nor increased serum ferritin levels to be predictive of infectious complications in hemodialysis patients. Serum ferritin levels between 500 and 800 ng/mL have been suggested as “safe” upper limits above which parenteral iron administration should be withheld. Evidence that dialysis patients’ risk of infectious or other complications is increased by iron administration that generates transient ferritin levels greater than 800 ng/mL, however, currently is not available. The extent to which elevated serum ferritin levels result from iron overload or, as part of an acute phase response, are indicative of other diseases processes should also be considered. Prospective comparisons of the long-term relative risks of IV dosing regimens have not yet been performed.

Concerns about possible cardiac toxicities of iron and about effects of lipid peroxidation that result from iron-induced generation of reactive oxygen species through the Haber-Weiss reaction continue to be subjects of active investigation. Iron therapy must be closely monitored so that it can be appropriately terminated when patients demonstrate increasing
serum ferritin or TSAT levels without additional erythropoietic benefit.

### Table 3. Possible Causes of Inadequate Response or Resistance to r-HuEPO

<table>
<thead>
<tr>
<th>Condition</th>
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<tr>
<td>Iron deficiency (absolute, functional)</td>
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<tr>
<td>Blood loss</td>
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<tr>
<td>Noncompliance with r-HuEPO administration (in patients who self-administer)</td>
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<tr>
<td>Infection, inflammation (clinically obvious, occult)</td>
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<tr>
<td>HIV infection</td>
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<tr>
<td>Hyperparathyroidism</td>
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<tr>
<td>Aluminum toxicity</td>
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<td>Folate or vitamin B₁₂ deficiency</td>
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<tr>
<td>Multiple myeloma, myelodysplastic syndromes</td>
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<tr>
<td>Other malignancy</td>
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<td>Hemoglobinopathies</td>
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<td>Hemolysis</td>
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<tr>
<td>Malnutrition</td>
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<tr>
<td>Inadequate dialysis</td>
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<td>ACE inhibitors, angiotensin receptor antagonists</td>
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ACE = angiotensin-converting enzyme.

- What problems may occur with r-HuEPO therapy?

### INADEQUATE RESPONSE

An inadequate response to r-HuEPO has been defined as failure to maintain target Hb and Hct levels despite IV administration of more than 450 U/kg/week or subcutaneous administration of 300 U/kg/week. Table 3 lists conditions that should be considered and treated when possible in patients who appear to be responding inadequately to r-HuEPO therapy. The most common causes of an incomplete or inadequate response to r-HuEPO therapy are an insufficient dose of r-HuEPO, noncompliance with r-HuEPO dosing in self-administering patients, and iron deficiency. The erythropoietic response to r-HuEPO is often impaired in inflammatory or infectious conditions, which may be clinically inapparent and suggested only by markers of activation of the acute phase response. Hypoalbuminemia (reflective of both nutritional and inflammatory status) and elevated C-reactive protein and serum ferritin levels (with a low-normal transferrin level) are predictors of impaired r-HuEPO responsiveness in dialysis patients. The suppressive effects of these inflammatory conditions on erythropoiesis are thought to be mediated by tumor necrosis factor-α, interleukin-1, interleukin-6, and possibly interferon-γ.

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor antagonists can reduce the erythrocytosis that occasionally follows renal transplantation, and ACE inhibitors have been reported to exacerbate anemia in hemodialysis patients not receiving r-HuEPO. This effect is thought to be mediated by a drug-induced decrease in endogenous erythropoietin production, although the precise mechanism is unclear. Whether ACE inhibitors and angiotensin receptor antagonists inhibit the response to exogenous r-HuEPO currently is uncertain. However, when present, this relatively minor effect may primarily involve patients on low doses of r-HuEPO and high doses of ACE inhibitors. Clinicians who consider stopping these drugs to enhance r-HuEPO responsiveness should also consider their cardiovascular benefits.

### ADVERSE EFFECTS

Reported adverse effects of r-HuEPO and increased Hb and Hct levels include development or exacerbation of hypertension, hemodialysis access thrombosis, seizures, increased heparin requirements during hemodialysis, reduced dialyzer clearance, and formation of antibodies to r-HuEPO. Adequately controlled studies are not available to fully assess the risk of access thrombosis related to r-HuEPO and increased Hb and Hct.
levels. In a prospective cohort study, Churchill et al\(^\text{10}\) observed an association between r-HuEPO treatment and an increased probability of prosthetic bridge graft but not native fistula thrombosis. Besarab et al\(^\text{21}\) recently reported an increased access thrombosis rate in both native arteriovenous fistulae and synthetic grafts in patients randomized to a normal Hct group, but they did not observe a correlation between access thrombosis and Hct level achieved. An increased thrombosis rate may result from direct or indirect effects of r-HuEPO or increased Hb and Hct levels on platelet function, endothelial function, or hemorheologic effects. Enhanced surveillance for access complications is not recommended for patients treated with r-HuEPO\(^\text{11,12}\).

The development of hypertension or exacerbation of pre-existing hypertension occurs in 20% to 35% of dialysis patients treated with r-HuEPO. The mechanisms for this effect are unclear but may include hemodynamic changes, effects of increased erythrocyte mass, and effects of r-HuEPO on vascular tone. Effects on vascular tone may be direct or result from release of or increased vascular responsiveness to catecholamines, endothelin, nitrous oxide, or vasoactive prostaglandins. In the Besarab et al study,\(^\text{21}\) blood pressures were comparable in the normal Hct and anemic control groups. Berns et al\(^\text{15}\) also did not observe a hypertensive effect at normal Hct levels in repeated interdialytic ambulatory blood pressure monitoring for up to 1 year in a small cohort of patients enrolled in the Besarab et al study.\(^\text{21}\) However, blood pressure should be monitored closely in all dialysis patients, with adjustments in antihypertensive medication, ultrafiltration goals, or both as appropriate.

A higher incidence of seizures compared with historical controls was noted in an early clinical trial of r-HuEPO,\(^\text{18}\) but subsequent data and clinical experience do not indicate an increased risk of seizures in patients receiving r-HuEPO.\(^\text{11,12}\) Likewise, heparin requirements and dialyzer clearance and reuse have not been shown to be consistently affected by r-HuEPO use, nor does there appear to be an adverse effect of r-HuEPO on renal function in patients with CRF who are not yet on dialysis. Formation of antibodies to r-HuEPO (4000 U subcutaneously 3 times weekly at each hemodialysis treatment) and iron dextran (50 mg IV once weekly during hemodialysis).

**OUTCOME OF CASE PATIENT**

The patient’s foot ulcer fails to heal, and a transmetatarsal amputation is performed. After completing a 3-week course of antibiotics, her surgical wounds have healed and she feels well and begins to ambulate. The patient has had no recent access complications and is maintaining an Hb level of 12 g/dL while receiving r-HuEPO (4000 U subcutaneously 3 times weekly at each hemodialysis treatment) and iron dextran (50 mg IV once weekly during hemodialysis).

**REFERENCES**