

# ANEMIA OF CRITICAL ILLNESS: PREVENTION AND TREATMENT



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## Learning Objectives

1. Detect the pathophysiologic cause(s) of anemia in critically ill patients and assess the risks associated with its development.
2. Assess for the presence of anemia of critical illness in patients using clinical and laboratory indicators.
3. Assess the risks and benefits associated with the various treatment strategies for anemia of critical illness.
4. Develop patient-specific therapeutic plans for the management of patients with, or at risk for developing, anemia of critical illness.
5. Formulate both pharmacological and nonpharmacological strategies to prevent anemia of critical illness and conserve the use of blood products.

## Introduction

Anemia is a frequent complication experienced by critically ill patients. In a series of 1136 patients, the Anemia and Blood Transfusion in Critical Care investigators found that 63% of patients admitted to intensive care units (ICUs) in Western Europe were anemic, defined as hemoglobin less than 12.0 g/dL. Nearly 33% of these patients had hemoglobin concentrations less than 10.0 g/dL on admission to the ICU. Others have found anemia to be present in as many as 75% of ICU patients. For patients admitted to the ICU without evidence of active bleeding, hemoglobin values have been shown to decrease by as much as 0.5 g/dL/day over the first several days of the ICU stay. In patients with persistent inflammatory states such as sepsis, the progressive decline in hemoglobin may continue beyond the first several days. Such reductions in hemoglobin

increase the severity of preexisting anemia and may ultimately lead to the development of anemia in patients with normal baseline hemoglobin values.

The presence of anemia in critically ill patients is associated with an increased use of blood products. In a study of about 5000 critically ill patients, investigators found that 44% of patients were transfused blood products during their stay in the ICU. Patients were transfused an average of  $4.6 \pm 4.9$  units of packed red blood cells (RBCs) with a mean pretransfusion hemoglobin of  $8.6 \pm 1.7$  g/dL. The majority of blood products were administered during the first week of the ICU stay, consistent with other studies. The quantity of blood product usage is troubling considering the risks associated with blood transfusions and the frequent shortages of blood supplies in recent years.

The use of blood products in critically ill patients is concerning because it is associated with increased morbidity and mortality. In the Anemia and Blood Transfusion in Critical Care study, hospital length of stay was increased in patients receiving transfusions compared with nontransfused patients ( $15.8 \pm 9.0$  days vs.  $10.9 \pm 7.9$  days;  $p < 0.001$ ). Transfused patients also had an increased length of stay in the ICU compared with those who did not receive transfusions (7.2 days vs. 2.6 days, respectively). Similarly, the authors found both ICU and overall mortality for patients receiving blood transfusions to be almost double that of nontransfused patients (ICU mortality 18.5% vs. 10.1%;  $p < 0.001$ ; overall mortality 29.0% vs. 14.9%;  $p < 0.001$ ). In critically ill patients with prolonged ICU stays, survival has been shown to be inversely related to the need for and quantity of transfused blood (81% for nontransfused patients, 67% for patients receiving 1–5 units of blood, 46% for patients receiving greater than 5 units of blood;  $p < 0.05$  for all comparisons).

Vincent JL, Baron JF, Reinhart K, et al. Anemia and blood transfusion in critically ill patients. *JAMA* 2002;288:1499–1507.

Corwin HL, Gettinger A, Pearl RG, et al. The CRIT study: anemia and blood transfusion in the critically ill—current clinical practice in the United States. *Crit Care Med* 2004;32:39–52.

## Abbreviations in this Chapter

CaO <sub>2</sub>	Arterial oxygen concentration
CI	Confidence interval
EPO	Erythropoietin
FFP	Fresh frozen plasma
ICU	Intensive care unit
IL	Interleukin
IRP	Iron regulatory protein
OR	Odds ratio
PaO <sub>2</sub>	Arterial pressure of oxygen in arterial blood
RBC	Red blood cell
rFVIIa	Recombinant activated factor VII
SaO <sub>2</sub>	Arterial oxygen saturation
TfR	Transferrin receptor

Because anemia is so prevalent in patients admitted to the ICU and is associated with an increased risk of morbidity and mortality, the prevention and treatment of anemia in these patients is critical. This chapter reviews the complex pathophysiology of anemia in critically ill patients, compares treatment options, and offers strategies aimed at preventing anemia of critical illness and minimizing the use of blood products.

## Pathophysiology

The etiology of anemia in critically ill patients is often multifactorial and may be the result of active bleeding, hemodilution, phlebotomy, hemolysis, inflammation, or more commonly some combination of these. Therefore, the pathophysiology of anemia in these patients is complex (Figure 1-1).

### Causes of Anemia in Critically Ill Patients

#### Active Bleeding

Active bleeding from the gastrointestinal tract, surgical sites, trauma, and other causes occurs in up to 40% of patients admitted to the ICU. Of importance, about 33% of blood transfusions in ICU patients are secondary to acute blood loss. The gastrointestinal tract is a frequent source of clinically significant bleeding complications in critically ill patients. Although clinically significant gastrointestinal tract bleeding (detected endoscopically) occurs in only 5%–6% of ICU patients, bleeding from the gastrointestinal tract accounts for about 33% of active bleeds that start in the ICU. Therefore, strategies such as stress-ulcer prophylaxis and early initiation of enteral feeding should be used to minimize the risk of developing bleeding from the gastrointestinal tract and subsequent anemia. Although perioperative and trauma-related bleeding play a role in the development of anemia in critically ill patients, the reader is

referred to the chapter titled “Special Considerations in the Management of Trauma Patients” for a more in-depth discussion on the pathophysiology and treatment of these causes of anemia.

#### Phlebotomy

An underappreciated cause of anemia in critically ill patients may be phlebotomy. In a series of 100 patients in whom phlebotomy practices were observed, the average number of daily blood samples obtained was 3 times greater in ICU patients than it was for patients located on general medical wards (3.4 blood samples/day in ICUs vs. 1.1 blood samples/day in general medical wards). Similarly, the average volume of blood loss due to phlebotomy was more than 3 times greater in the ICU patients. In critically ill patients with arterial lines, the frequency of blood sampling and the total volume of blood loss was even greater.

Several analyses have shown that ICU patients lose about 41 mL/day of blood secondary to phlebotomy; however, some have estimated daily phlebotomy-related blood loss as high as 70 mL/day. The overall total volume of blood loss due to phlebotomy in ICU patients is highly variable and appears to be positively correlated to the duration of ICU stay and the quantity of blood transfusions required. Several analyses suggest that overall total volume of blood loss ranges between 600 mL and 2200 mL over the course of a hospitalization in critically ill patients. Phlebotomy accounts for about 20% of total blood loss in these patients. In addition, as much as 30% of the overall volume of transfused blood products in critically ill patients is due to phlebotomized blood loss.

Therefore, as clinical pharmacists, we must consider phlebotomized blood loss when devising monitoring plans for the pharmacotherapy of critically ill patients. Pharmacists must be judicious in their recommendations regarding blood sampling to maximize efficiency and minimize the risk of precipitating or worsening underlying anemia from the blood draws suggested.

#### Inflammation (Anemia of Critical Illness)

In about 50% of critically ill patients with more profound anemia (hemoglobin less than 10 g/dL), an identifiable cause (e.g., history of anemia or acute blood loss) is not often present. This is often defined as anemia of critical illness. Inflammation that occurs in the setting of trauma, surgery, and sepsis, for example, is believed to play a significant role in the pathogenesis of anemia of critical illness. The pathophysiology is complex but appears to be triggered by the release of various inflammatory cytokines leading to decreased heme synthesis, increased heme degradation, decreased RBCs survival, and ultimately anemia of critical illness.

#### Regulation of Erythropoiesis

Erythropoietin (EPO) is a glycoprotein hormone that serves as the primary regulator of erythropoiesis, the production of RBCs (Figure 1-2). In response to hypoxia, decreased oxygen delivery capacity, and decreasing

Smoller BR, Kruskall MS. Phlebotomy for diagnostic laboratory tests in adults. Pattern of use and effect on transfusion requirements. *N Engl J Med* 1986;314:1233–5.

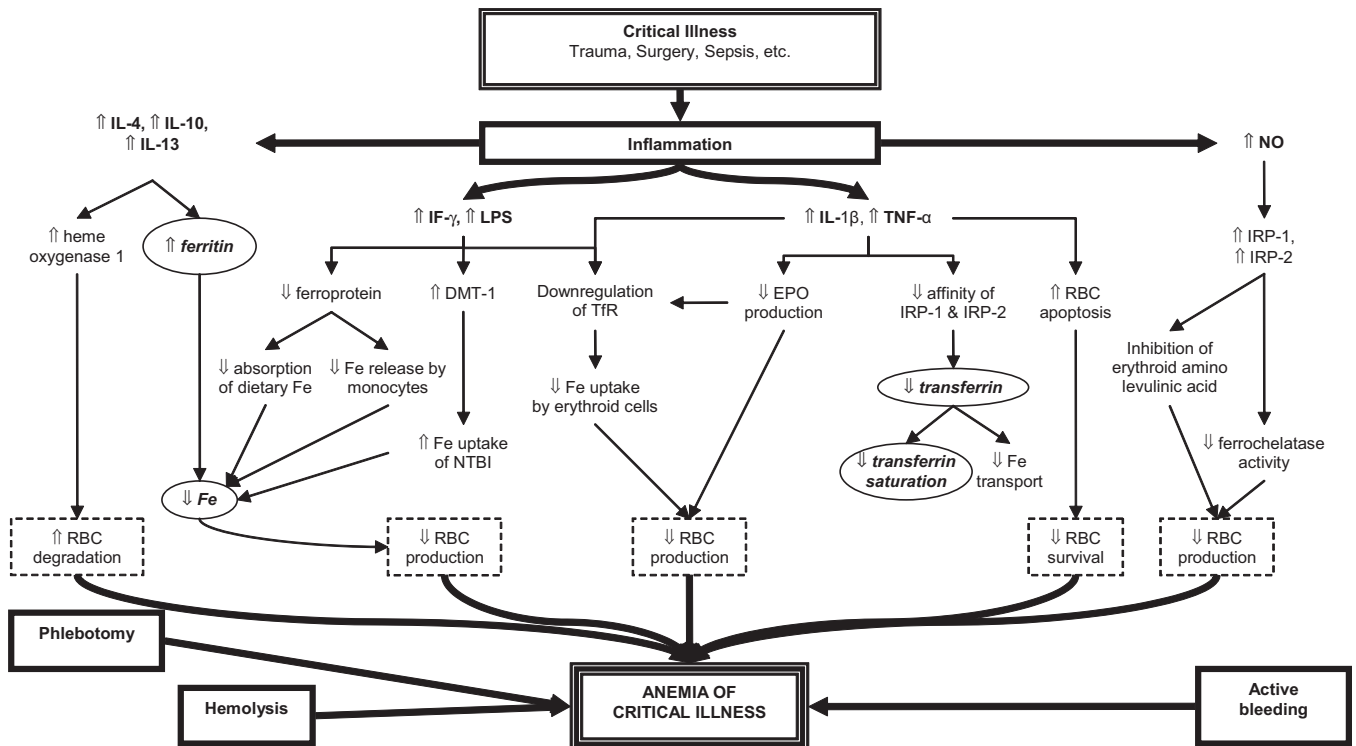


Figure 1-1. Pathogenesis of anemia of critical illness.

Factors and/or conditions associated with the development of anemia of critical illness are displayed within the dark solid boxes. Laboratory abnormalities commonly seen in patients with anemia of critical illness are bolded, italicized, and encircled in dark solid ovals. The byproducts of the various inflammatory pathways thought to contribute to the development of anemia of critical illness are shown in the dashed boxes.

DMT = divalent metal transporter; EPO = erythropoietin; Fe = iron; IF = interferon; IL = interleukin; IRP = iron regulatory protein; LPS = lipopolysaccharide; NO = nitric oxide; NTBI = non-transferrin-bound iron; RBC = red blood cell; TfR = transferrin receptor; TNF = tumor necrosis factor.

hemoglobin, EPO production increases exponentially to stimulate production of RBCs. This hormone is produced primarily in the peritubular interstitial cells of the renal cortex as well as in parenchymal hepatocytes. Erythropoietin binds to EPO receptors on erythroid progenitor cells. In response to EPO, these progenitor cells further differentiate into burst-forming unit erythroid cells and colony-forming unit erythroid cells. These cells then differentiate into erythroid precursors and proerythroblasts, followed by differentiation to erythroblasts and reticulocytes, and eventually to mature erythrocytes.

Iron is used by erythroid cells during erythropoiesis and EPO is believed to play a role in iron metabolism. Dietary iron is absorbed in the small intestine and bound to transferrin, an iron-transporting protein. Transferrin binds to the transferrin receptor (TfR) on erythroid cells, allowing these cells to take up iron from transferrin. During the final step of erythropoiesis, the enzyme ferrochelatase inserts iron into the protoporphyrin IX ring, allowing oxygen transport by hemoglobin and myoglobin. Excess iron binds to ferritin and is stored intracellularly. Iron metabolism is regulated by the iron regulatory proteins (IRP)-1 and -2. These proteins regulate the storage, consumption, and uptake of iron.

There is some evidence that EPO may play a role in iron metabolism as well. In vitro studies have shown that EPO activates IRP-1. Consequently, iron uptake may be enhanced via the TfR while iron storage is reduced secondary to decreased ferritin production.

#### Impaired Erythropoiesis in Critically Ill Patients

**Inadequate Erythropoietin Production.** One of the hallmark features of anemia of critical illness is a blunted response of endogenous EPO. Several studies have investigated the EPO response in critically ill patients. In each case, the EPO response to anemia was significantly decreased. In one study, 36 critically ill patients with anemia were compared to 18 otherwise healthy patients with iron-deficiency anemia. Baseline hematocrit concentrations were similar between the two groups (about 30%). Although EPO concentrations were above normal (defined as 6–32 units/L) in both groups, the critically ill patients had significantly lower EPO concentrations than those in the control group. In fact, the EPO concentrations were 4–8 times greater in the control patients than in those who were critically ill. The EPO response appeared to be impaired more in patients with acute renal failure or sepsis. Similar results have been shown in postoperative and

Rogiers P, Zhang H, Leeman M, et al. Erythropoietin response is blunted in critically ill patients. *Intensive Care Med* 1997;23:159–62.

trauma patients.

In experimental models, interleukin (IL)-1 $\beta$  and tumor necrosis factor- $\alpha$  have decreased EPO production. Because these inflammatory cytokines are released in response to trauma, surgery, and sepsis, they are believed to play a major role in the impaired erythropoietic response in critically ill patients with anemia (Figure 1-1).

**Altered Iron Metabolism.** Several inflammatory cytokines disrupt normal iron metabolism. Tumor necrosis factor- $\alpha$ , IL-1 $\beta$ , and IL-6 all cause an increase in ferritin production, leading to increased iron storage. Divalent metal transporter-1 may play a role in this process. The cytokines interferon- $\gamma$  and lipopolysaccharide have been shown to increase divalent metal transporter-1 activity, increasing uptake of non-transferrin-bound iron and decreasing serum iron levels. Interferon- $\gamma$  and lipopolysaccharide also cause a downregulation of ferroprotein, decreasing the release of iron from monocytes and potentially decreasing absorption of dietary iron, both of which lead to decreased iron levels and impaired erythropoiesis. In addition, the binding affinity of IRP-1 and IRP-2 are impaired, altering iron metabolism.

The TfRs play a major role in iron metabolism and are dysfunctional in the presence of inflammation. The inflammatory mediators tumor necrosis factor- $\alpha$ , IL-1 $\beta$ , IL-4, IL-6, IL-10, IL-13, interferon- $\gamma$ , and lipopolysaccharide all

cause a downregulation of TfRs. Consequently, iron uptake by erythroid cells is decreased, iron storage (in the form of ferritin) is increased, serum iron levels are decreased, and erythropoiesis is impaired.

Nitric oxide also may play a role in altered iron metabolism in patients with anemia of critical illness. Inflammatory states such as sepsis lead to increased nitric oxide production. Nitric oxide inhibits erythroid amino-levulinic acid, decreases iron consumption, and decreases ferrochelatase activity, inhibiting the final step in erythropoiesis.

### Decreased RBC Life Cycle

In critically ill patients, not only is erythropoiesis impaired, but also the normal life cycle of RBCs is decreased. Normally, the lifespan of RBCs is about 120 days. However, in inflammatory states, tumor necrosis factor- $\alpha$  and IL-1 $\beta$  have decreased erythrocyte survival. In addition, oxidative stress from the inflammatory state likely plays a role in this process by inducing RBC apoptosis.

Other factors contribute to the decreased lifespan of RBCs. Interleukin-10 has increased heme oxygenase-1 activity, leading to increased RBC degradation. This cytokine is increased in patients who are critically ill, and it also has been implicated in the pathophysiology of anemia

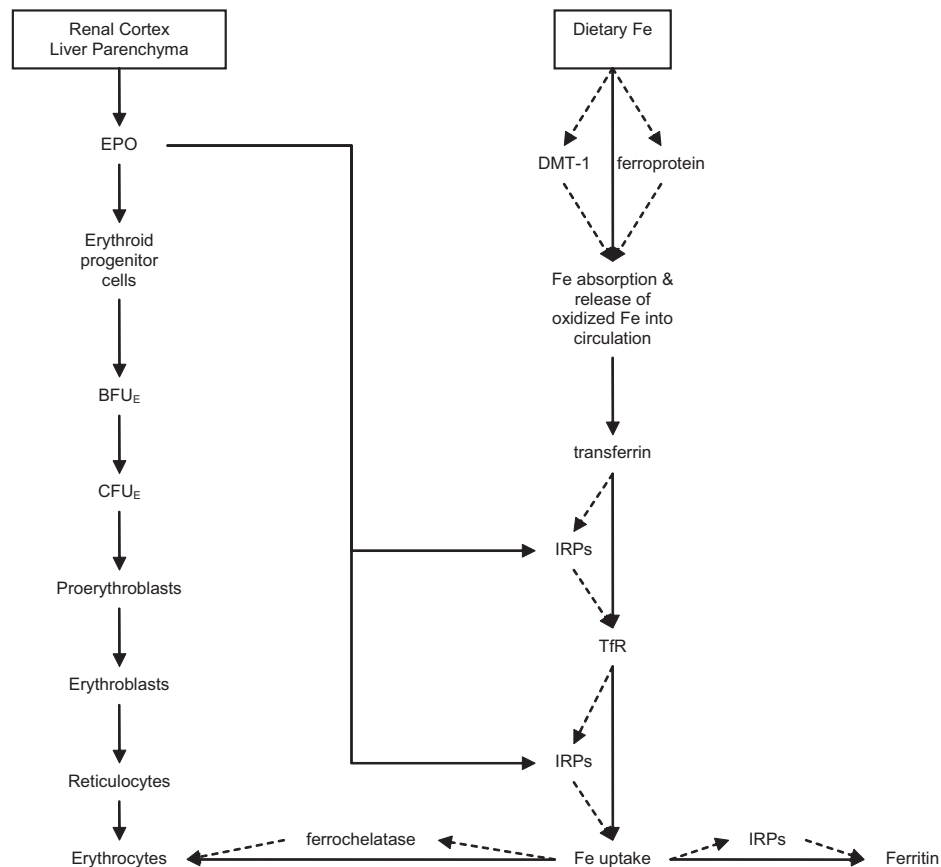


Figure 1-2. Regulation of erythropoiesis and iron metabolism. Dashed lines indicate these mediators regulate the corresponding cascade.

BFU<sub>E</sub> = burst-forming-unit erythroid; CFU<sub>E</sub> = colony-forming-unit erythroid; DMT = divalent metal transporter; EPO = erythropoietin; Fe = iron; IRP = iron regulatory protein; TfR = transferrin receptor.

of critical illness. Hemolysis can also occur in critically ill patients secondary to several inherited and acquired disorders. In addition, several therapeutic measures common to ICU patients are known to cause hemolysis, such as transfusion reactions, rapid infusion of hypotonic solutions, and use of invasive devices such as intra-aortic balloon pumps, ventricular assist devices, and extracorporeal circulation. When coupled with impaired erythropoiesis, the abbreviated RBC lifespan seen in critically ill patients has a significant role in the pathogenesis of anemia of critical illness.

### Exacerbating Factors

The mechanism of anemia of critical illness is attributed, for the most part, to a dysfunctional EPO response and impaired erythropoiesis secondary to inflammation. Nonetheless, many exacerbating factors may affect the development and severity of anemia, adding to the difficulties encountered while attempting to ameliorate this condition. Excluding gross hemorrhage, two major exacerbating factors that can affect these patients are coagulopathies and certain nutritional deficits. Each factor may contribute to the development of anemia of critical illness, either directly or through a more subtle effect on the disease process.

### Coagulopathy

Coagulopathy is a commonly encountered problem both on admission to the ICU and during ICU treatment. Broadly speaking, coagulopathies are the result of a dysfunctional clotting cascade. Coagulopathies may also be secondary to a dysfunction or relative lack of platelet function.

Coagulopathy in critically ill patients has numerous causes. Chronic disease states that cause hepatic or renal dysfunction may cause coagulopathies. Similarly, cancer and hemophilia may be associated with coagulopathic states. In the ICU, the coagulopathies can be broken down into five groups: inherited (e.g., hemophilia), consumptive (e.g., disseminated intravascular coagulation), vitamin K dependent (e.g., liver disease, vitamin K deficiency, and warfarin), iatrogenic (e.g., heparin toxicity/overdose and volume overload), and platelet dysfunction (e.g., aspirin therapy, uremia, or idiosyncratic thrombocytopenic purpura). Many of these causes are not easily preventable, and those involving pharmacological drugs can be some of the most challenging to control.

Coagulopathy can, at times, be difficult to control in a critically ill patient, leading to further blood loss and worsening anemia. Although coagulopathies per se do not cause hemorrhagic events, they are capable of greatly exacerbating blood loss and making control of large hemorrhages more challenging. Coagulopathies may also exacerbate small traumatic events that result in small volumes of blood loss. Over an extended time period, these relatively small bleeding complications can lead to a significant amount of hemorrhage. An example of this would be postoperative patients experiencing hemorrhage from wounds, both external and internal. Also, coagulopathies limit the ability of the medical team to perform needed interventions such as the insertion of central lines, peripherally inserted central catheters, and extraventricular drains because of the increased risk of

hemorrhage during and following the procedure.

**Nutritional and Pharmacological Vitamin K Deficiency.** One of the easiest causes of coagulopathy to identify is nutritional vitamin K deficiency. For patients with an elevated prothrombin time or international normalized ratio, a simple trial with parenteral or oral vitamin K can rule out deficiency. Although risks are associated with different administration routes of vitamin K, administering 10 mg/day for 3 days can exclude the deficiency as the cause of the coagulopathy. Caution should always be used when administering vitamin K via the intravenous route secondary to the risk of severe hypotension. It should never be administered rapidly by the intravenous route. An acceptable method to administer intravenous vitamin K is to dilute 10 mg in 50 mL of normal saline or dextrose 5% and administer this solution over 30 minutes. Absorption via the subcutaneous route can be problematic, especially if the patient is experiencing hemodynamic compromise and decreased peripheral perfusion. Absorption issues may also be a factor with the oral route in patients with decreased gastrointestinal perfusion or following abdominal surgery. Other parameters such as liver disease should be more carefully evaluated.

A more severe iatrogenic depletion of vitamin K-dependent factors could be secondary to the administration of the anticoagulant warfarin. Warfarin is a potent inhibitor of the activation of vitamin K-dependent clotting factors II, VII, IX, and X. Because of its narrow therapeutic index, warfarin is one of the leading causes of adverse drug reactions requiring hospitalization. Many of these events are life-threatening, not directly from the coagulopathy, but from the trauma that many of these patients experienced (e.g., secondary to falls) before admission to the ICU or hospitalization. Small, but disastrous, intracranial hemorrhages can occur in these patients, leading to significant morbidity and mortality. Significant gastrointestinal hemorrhaging can also develop, leading to anemia.

**Drug-Induced Platelet Dysfunction.** Therapy with aspirin, clopidogrel, or a combination of both is commonly encountered in patients admitted to ICUs. Aspirin is effective in disrupting platelet aggregation by irreversibly inhibiting platelet cyclooxygenase-1. The inhibition of platelet cyclooxygenase-1 in turn leads to a decrease in the production of thromboxane A<sub>2</sub>, a potent platelet aggregating factor. Because platelets have the inability to synthesize cyclooxygenase-1 once inhibited by aspirin, thromboxane A<sub>2</sub> is therefore not synthesized and the platelets lose aggregating capabilities for the life span of the platelet. Clopidogrel is a thienopyridine that irreversibly inhibits adenosine 5' diphosphate receptors on the cell surface of platelets. The thienopyridines are more potent antiplatelet drugs than aspirin and may prolong bleeding times in patients. Because of the ability of these drugs to cause coagulopathies via the inhibition of platelet aggregation, patients treated with thienopyridines who require surgical interventions are at an increased risk of bleeding.

### Nutritional Deficits

Adequate nutrition is sometimes difficult to achieve in critically ill patients, leading to significant nutritional

deficiencies. Patients presenting to the ICU may also be significantly malnourished as a result of their acute illness or other comorbid conditions. The lack of appropriate enteral access, gastrointestinal dysfunction, and surgery are all obstacles for adequate nutrition in the ICU. In addition, nutrition is a factor commonly overlooked by the health care team. Patients may remain unfed for days secondary to invasive tests, planned procedures, and surgery, thus setting the stage for significant caloric and protein deficits. Critically ill patients may have altered gastrointestinal absorption of critical vitamins and minerals. A deficit of those vitamins and minerals important for the production and function of RBCs may contribute to the development of anemia.

**Iron Deficiency.** Iron, cobalamin (vitamin B<sub>12</sub>), and folate are the three most critical nutrients for erythropoiesis. Deficiencies of these nutrients can cause significant anemias. Because iron is responsible for the oxygen-carrying capacity of hemoglobin, it is the most critical elemental nutrient in the body. Adult hemoglobin, as a molecule, is composed of four globin proteins. Two of these globins are known as the alpha globins, and the remaining two are known as the beta globins. A heme molecule with iron at its center is connected to each of the globin proteins. Thus, every molecule of hemoglobin contains four molecules of iron and is capable of binding four molecules of oxygen. Because hemoglobin gives erythrocytes their pigment, as hemoglobin production decreases because of iron deficiency, the cells become hypochromic. Erythrocytes of patients with iron deficiency anemia also tend to be smaller than those of patients who are not iron deficient. Thus, iron deficiency anemia is traditionally known as a microcytic, hypochromic anemia. When the erythrocytes are already presenting in a microcytic, hypochromic state, the iron stores have generally been depleted for some time.

Because of the important role of iron, the body has an intricate system of storage and transport of this elemental nutrient. For hemoglobin production to continue normally, an adult requires about 25 mg/day of iron. Surprisingly, only 1–2 mg of this amount is derived from dietary absorption. The vast portion of iron in the body is recycled by the reticuloendothelial macrophage system and reused once erythrocytes have reached their life expectancy. The primary storage place for iron (in the form of ferritin) is the liver. However, iron is also stored throughout the body, and large concentrations can be found in muscle tissue in the form of myoglobin.

**Other Nutritional Deficiencies.** Vitamin B<sub>12</sub> and folate are two cofactors responsible for DNA synthesis. In terms of erythropoiesis, a deficiency of vitamin B<sub>12</sub> or folate can lead to a delay in the maturation of the erythrocytes in the bone marrow. Because of this delay in DNA maturation, the cells tend to appear macrocytic, and thus cobalamin and folate deficiencies are considered macrocytic anemias. Poor diet, malabsorption, and alcoholism are common causes of this type of anemia. Fortunately, this form of anemia is readily reversible with supplementation of the deficient nutrient(s).

The diagnosis of cobalamin deficiency is particularly important in the ICU because of the neurological sequelae that may ensue if the deficiency remains untreated.

**Impact of Nutritional Deficiencies.** To elucidate the nutritional deficiencies of critically ill patients on presentation to the ICU, a study in three academic medical center ICUs was performed to determine the factors that contribute to inappropriate erythropoiesis in this population, including nutritional deficiencies. The analysis was done in conjunction with a trial that examined the role of erythropoietin in ICU patients with anemia. The nutritional deficiencies examined were iron, vitamin B<sub>12</sub>, and folate. Patients were screened for these deficiencies on day 2 or day 3 of their ICU stays. Of the 160 patients evaluated in the study, 13% had some form of a correctable nutritional deficiency, 9% presented with iron deficiency, and 2% presented with vitamin B<sub>12</sub> and folate deficiencies each. The authors also found that most of their subjects had low serum iron concentrations, low total iron-binding capacities, low serum iron to total iron-binding capacity ratio, and elevated ferritin levels. The authors suggested that, at the time of screening (ICU days 2 and 3), patients displayed characteristics consistent with anemia of chronic disease.

This study does not shed light on the nutritional deficiencies of prolonged stays or the varying degrees of nutritional deficiencies of patients in the ICU. Because these evaluations were drawn on ICU days 2 and 3, it is difficult to draw conclusions on the nutritional deficiency of iron, vitamin B<sub>12</sub>, and folate in patients with prolonged ICU stays. Although the overall rates of folate and Vitamin B<sub>12</sub> deficiencies in this trial seem low, certain patient populations may be at greater risk for these deficiencies. For example, B<sub>12</sub> deficiency has a high prevalence in geriatric patients, with some estimates as high as 15% in this patient population. In addition, patients who have undergone gastric bypass surgery are also at risk for significant deficiencies in folate and B<sub>12</sub>. If underlying nutritional deficiencies are suspected, more thorough nutritional assessments may be necessary, especially if anemia is present.

### Complications of Anemia in Critically Ill Patients Inadequate Tissue Oxygenation

Anemia impairs the body's ability to oxygenate the vital organs. Oxygen is transported in the blood in two forms: bound to hemoglobin and dissolved in plasma. In healthy individuals, greater than 98% of oxygen is bound to hemoglobin; the remainder is dissolved in plasma. The arterial oxygen concentration (CaO<sub>2</sub>) of the blood is best described by the following equation:

$$\text{CaO}_2 = (\text{SaO}_2 * 1.39 * \text{hemoglobin}) + (0.0031 * \text{PaO}_2)$$

where SaO<sub>2</sub> is arterial oxygen saturation (oxygen bound to hemoglobin) and PaO<sub>2</sub> is the partial pressure of oxygen in arterial blood (oxygen dissolved in plasma). When hemoglobin falls, CaO<sub>2</sub> falls by a similar magnitude. For example, for a patient with a SaO<sub>2</sub> of 98% and a PaO<sub>2</sub> of 100 mm Hg, when the hemoglobin is 15 g/dL, the CaO<sub>2</sub> is

Rodriguez RM, Corwin HL, Gettinger A, et al. Nutritional deficiencies and blunted erythropoietin response as cause of the anemia of critical illness. *J Crit Care* 2001;16:36–41.

20.3 mL oxygen/100 mL (normal = 16–22 mL oxygen/100 mL). However, when hemoglobin falls to 8 g/dL (47% decrease), the  $\text{CaO}_2$  decreases by 46% to 11 mL oxygen/100 mL, significantly lower than normal, resulting in hypoxia and impaired tissue oxygenation. Hypoxia may also develop in the presence of decreased oxygen delivery (e.g., ischemia or low cardiac output), decreased arterial oxygen saturation (e.g., impaired oxygen exchange in the lungs), and increased oxygen consumption (e.g., sepsis).

Fortunately, the body adapts quickly to anemia by increasing cardiac output and increasing oxygen extraction. In euvoletic patients, anemia causes a decrease in blood viscosity, which leads to an increase in cardiac output secondary to decreased blood viscosity. However, if volume status changes (e.g., hypovolemia or volume overload occur), increases in heart rate and/or contractility occur to maintain normal cardiac output at the expense of increased oxygen consumption. In addition, several compensatory mechanisms improve the efficiency of oxygen use, leading to an increased extraction of oxygen by the tissues.

As anemia worsens and/or the adaptive mechanisms fail, both oxygen delivery and consumption eventually decrease, leading to tissue hypoxia. Inadequate tissue oxygenation, if prolonged, may lead to cerebral ischemia, myocardial ischemia, multiorgan failure, lactic acidosis, and death.

### Cardiovascular Complications

For patients with anemia of critical illness, cardiovascular morbidity and mortality are a major concern as many of these patients have cardiovascular comorbid conditions such as ischemic heart disease. Indeed, hematocrit values less than 28% have been associated with electrocardiographic evidence of myocardial ischemia and increased incidence of major adverse cardiac events in patients undergoing peripheral vascular surgery and radical prostatectomy. In addition, several studies conducted in surgical patients demonstrated that mortality is inversely related to hemoglobin. Similarly, hematocrit has been shown to be inversely related to the development of shock, heart failure, need for blood transfusion, length of hospital stay, and mortality.

The available evidence consistently shows that anemia increases the risk of major adverse cardiac events in critically ill patients with known cardiovascular disease. Less certain is the critical threshold at which the risk of cardiac events increases, particularly in the absence of known cardiovascular disease. The risk of cardiac morbidity and mortality appears to increase most in patients with a hematocrit less than 28% and hemoglobin concentrations less than 8–10 g/dL. However, the risks are likely greater in patients with known cardiovascular disease than in patients without heart disease. For example, the risk of anemia-related cardiac events is likely lower in an otherwise young, healthy adult than in an elderly patient with a significant history of underlying cardiovascular disease. Therefore, the critical threshold probably varies according to patients' underlying risk for major adverse cardiac events, with higher thresholds for patients with known cardiovascular disease.

## Diagnosis of Anemia of Critical Illness

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### Clinical Assessment

The diagnosis of anemia in the ICU requires both clinical and laboratory assessments. Clinically, the symptoms of anemia determine the severity of illness and are secondary to a decrease in oxygen delivery to vital tissues. As such, generalized complaints of fatigue or shortness of breath may be useful to assess the severity of decreased oxygen delivery. Other symptoms such as mental status changes may be a sign of cerebral hypoxia. However, mental status changes are at times difficult to assess in critically ill patients because multiple factors can contribute to an altered sensorium. Physical examination might be helpful for detecting some causes of gross hemorrhage or evidence of heart failure. Radiological evaluation might also be warranted in trauma or postoperative patients to identify internal bleeding sources. Lastly, in assessing the severity of anemia, invasive hemodynamic monitoring with a pulmonary artery catheter may be useful in determining not only the hemodynamic status, but also the tissue oxygenation in critically ill patients. All in all, the diagnosis of anemia in ICU patients is difficult to make on clinical examination alone and should be made in conjunction with laboratory assessment.

### Laboratory Assessment

Laboratory assessment in critically ill patients is the most reliable tool to make the diagnosis of anemia and, perhaps, to determine its etiology. First and foremost, the hemoglobin concentration is the most useful hematological assessment made in critically ill patients. Normal values for adult men are 13–18 g/dL and for adult women 12–16 g/dL. The diagnosis of anemia is often made if hemoglobin concentrations fall below these ranges. When monitoring hemoglobin concentrations, it is imperative to monitor trends, which allow clinicians to diagnose more subtle forms of blood loss that a patient may experience. Monitoring trends can also limit the amount of transfusions administered by monitoring the overall clinical picture and correlating that with a tolerable concentration of hemoglobin. Another important consideration when evaluating the hemoglobin concentration is the hydration status of the patient. Patients who are volume-overloaded may exhibit a decrease in their hemoglobin concentration. The “anemia” in this case is not due to impaired erythropoiesis or blood loss. It is a dilutional effect from excess intravascular fluid and usually requires no intervention other than decreasing the hydration of the patient to achieve a euvoletic state. Patients who are dehydrated when presenting to the ICU may have normal or slightly elevated hemoglobin concentrations that promptly return to baseline with fluid resuscitation. Inexperienced clinicians will occasionally mistake this decrease as a hemorrhagic event, obtain unnecessary diagnostic tests, and administer unnecessary treatments.

Once the diagnosis of anemia has been made, the next step is to determine, if possible, the cause of anemia. An



examination of the erythrocyte morphology is thus warranted. The mean corpuscular volume is an indication of the RBC size. The normal range is 81–99 fl. Volumes less than 80 fl are considered microcytic and may be indicative of iron deficiency anemia. Other microcytic anemias include anemia of chronic disease, thalassemia, and copper deficiency. If the mean corpuscular volume is greater than 100 fl, a macrocytic anemia is present. Common causes of macrocytic anemias include deficiencies in either vitamin B<sub>12</sub> or folate, hyposplenism, and liver disease. Normocytic anemias, with normal mean corpuscular volumes, may also be present. Examples of normocytic anemias are anemia of chronic disease and anemia of renal failure.

A useful test in the ICU to determine if patients are experiencing an adequate erythropoietic response to anemia is the reticulocyte count. Reticulocytes are immature erythrocytes. Evaluating the reticulocyte count allows clinicians to determine the functionality of the bone marrow. Simply stated, the erythropoietic response to anemia causes an increased production of erythrocytes. Patients with an intact hematopoietic system should respond by displaying an increase in the reticulocyte count. Similarly, in response to treatment (e.g., supplementation with iron, vitamin B<sub>12</sub>, or folate; treatment with epoetin alfa), patients should display an increase in their reticulocyte count. In patients with evidence of impaired erythropoiesis (e.g., decreased reticulocyte count), an EPO concentration may be useful to determine the cause of decreased hematopoiesis. In critically ill patients with anemia and low or normal reticulocyte counts, the hematopoietic response may be impaired and may suggest other causes such as anemia of critical illness.

If microcytic anemia is diagnosed, it is necessary to evaluate the iron status of the patient. A serum iron concentration should be low in a patient with iron deficiency anemia. In the presence of acute inflammatory processes that disrupt normal iron metabolism, serum iron concentrations can also be decreased. Because iron in the body is stored in the form of ferritin, a ferritin concentration gives a good picture of overall iron stores and is the most useful test in determining iron deficiency. In iron deficiency anemia, ferritin is usually decreased. However, in inflammatory states, normal iron metabolism may be disrupted, resulting in elevated ferritin concentrations. Therefore, elevated ferritin concentrations may be indicative of either chronic inflammatory causes of anemia (e.g., anemia of chronic disease) or anemia of critical illness. Total iron-binding capacity is an indication of how well iron is binding to transferrin. In iron-deficient anemia, this value is elevated. However, total iron-binding capacity is not a sensitive marker. In the presence of inflammation, it may appear low. In addition, the ratio of serum iron to total iron-binding capacity may appear low in anemia of critical illness. Lastly, transferrin saturation may be helpful in diagnosing either overt or functional iron deficiency (e.g., anemia of critical illness). In patients with anemia of critical illness, the transferrin saturation is generally low (less than 20%). Although iron studies provide valuable information regarding the cause of anemia in the ICU, the

interpretation of iron studies in a critically ill patient should be done with caution because of the multiple confounding factors. However, iron studies may provide information that might assist in determining the type of anemia a patient is experiencing.

## Treatment

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### Therapeutic Goals

#### Maintain Adequate Tissue Oxygenation and Perfusion

Critically ill patients with anemia have increased morbidity and mortality. The untoward events associated with anemia of critical illness are undoubtedly related to impaired tissue oxygenation leading to organ dysfunction, organ failure, and death. Therefore, the primary goal in critically ill patients with anemia is to maintain adequate tissue oxygenation and perfusion to prevent tissue hypoxia, ischemia, and organ dysfunction or failure.

#### Immediate Correction of Severe Anemia

Because anemia is associated with an increased risk of morbid events, there is a lot of discussion regarding the “critical hemoglobin concentration,” or the hemoglobin concentration at which the energy production of cells is dependent on the oxygen supply. In theory, below this hemoglobin concentration, oxygen delivery is impaired, tissue hypoxia ensues, and the risk of adverse outcomes increases. This threshold also serves as a theoretical trigger for administering blood products. Although there is no universal agreement as to the appropriate critical hemoglobin value in critically ill patients, immediate correction of severe anemia (i.e., hemoglobin less than 7.0 g/dL) is another goal when treating anemia of critical illness.

#### Prevent and Minimize Blood Loss

Anemia of critical illness has a complex pathophysiology. Nevertheless, blood loss plays a large role in the development and manifestations of anemia of critical illness. In many cases, blood loss is correctable. Therefore, prevention and minimization of blood loss is the third goal when treating critically ill patients with or without anemia.

#### Blood Product Administration

The concept of the enclosed circulatory system, first proposed by William Harvey in the early 17th century, opened the door for the science of transfusion medicine. For the past few decades, the administration of blood products has been one of the mainstays of therapy for anemia in critically ill patients. However, maintaining a supply of blood products in the face of increased demand is a challenge faced by the nation’s blood banks. Despite aggressive public relations campaigns encouraging blood donation, supply problems continue to be an issue encountered daily for many hospitals throughout the country.

#### Safety of Blood Product Administration

While lifesaving at times, blood transfusions are not a fail-safe method for treating anemia. Blood transfusions are



still wrought with a significant amount of risk. Some of these risks include the transmission of infectious pathogens, volume overload, iron overload, and immune-mediated reactions. The transmission of infections from transfusions remains a major concern. Currently, the donated blood supply is screened for the presence of the human immunodeficiency virus-1 and -2, human T-cell lymphotropic virus-1, hepatitis B virus, hepatitis C virus, and syphilis. A multitude of other safety factors are also used to minimize risk to recipients. In general, the risk of contracting active disease from one of these pathogens during a transfusion is low. However, contracting a bacterial infection during a transfusion is a real risk and is encountered often in patients in the ICU. Although blood products that harbor bacteria are an obvious source for bacterial infection, there is emerging evidence that the transfusion of blood products may affect immunomodulation. Many mechanisms for this phenomenon have been proposed that seem to implicate allogenic leukocytes, allogenic plasma components, or substances accumulated in the product during storage for the immunodepressant effects seen in the recipient. In addition, new pathogens (e.g., West Nile virus) are always emerging, further complicating the efforts to protect the blood supply and the patients receiving transfusions.

Immune-mediated reactions can be one of the most dangerous types of reactions encountered by blood transfusion recipients. Some of the immune reactions possibly encountered include febrile reactions, hemolysis, and anaphylaxis. Febrile reactions are the most common reaction experienced by patients. If the transfusion is thought to be causing the fever, it should be stopped immediately and the adverse event should be reported to the blood bank. Antihistamines are not effective in treating or preventing this type of reaction. Rather, these reactions can be prevented or treated with acetaminophen. Meperidine is also an option for patients experiencing rigors or chills. Hemolytic reactions, which rarely cause symptoms and which are often found serendipitously, can be dangerous and even lead to the patient's death. Patients experiencing hemolysis can develop fever and chills and can also experience hemoglobinuria or renal failure. Patients may also complain of pain. Anaphylaxis is another concern with administration of blood products and can result from relatively small volumes of transfused blood. Prompt discontinuation of the transfusion and supportive measures are warranted to treat hypotension or shock, should they occur.

Volume overload is a commonly encountered occurrence in the ICU secondary to the volume of blood products administered. For example, one unit of packed RBCs corresponds to about 250 mL of volume. Patients at risk for volume overload from transfusions include patients with heart failure or renal failure. Signs may manifest as decreased oxygenation, pulmonary edema, peripheral edema, and even atrial fibrillation. The use of loop diuretics concomitantly with administration of blood products may

decrease the risk of volume overload in high-risk patients receiving a large transfusion volume.

### Therapeutic Administration of Blood Products

In terms of therapeutics, there is considerable debate as to when to initiate blood transfusions in critically ill patients. For many critical care clinicians, the historical threshold for initiating a transfusion is a hemoglobin value less than 10 g/dL. This number was mainly adapted from studies in perioperative patients in an attempt to maximize oxygen delivery. In the Transfusion Requirements in Critical Care study, the critical threshold for transfusions in critically ill patients with anemia was investigated. More than 800 critically ill patients were randomized to either a liberal transfusion group (transfusion trigger: hemoglobin less than 10 g/dL, goal hemoglobin 10–12 g/dL) or a restrictive group (transfusion trigger: hemoglobin less than 7 g/dL, goal hemoglobin 7–9 g/dL). All-cause mortality at 30 days was not significantly different between groups. Of note, this study was unblinded, which may have biased the treatment of patients. However, the use of vasoactive drugs, antibiotic drugs, and Swan-Ganz catheters was not significantly different between the groups. This study suggests that critically ill patients may be able to tolerate much lower hemoglobin concentrations than previously thought without significant consequences. Studies in Jehovah's Witnesses found that the patients were able to tolerate surgeries despite hemoglobin concentrations less than 8 g/dL with minimal blood loss during the surgery and that mortality did not increase until hemoglobin concentrations were less than 5 g/dL.

In summary, no consensus regarding the hemoglobin threshold definitively indicates the need for transfusion therapy unless severe anemia is present (i.e., hemoglobin less than 7 g/dL). Although maintaining a hemoglobin concentration above 10 g/dL in all critically ill patients is a strategy that may be appropriate for some patient subgroups (e.g., significant cardiac disease), it may not be feasible or necessary for all critically ill patients. Also, considering the risks, cost, and relative shortage of blood products, limiting transfusions may be more beneficial to the patient. Ultimately, the decision to transfuse cannot be based on one parameter such as hemoglobin. Rather, it should be based on clinical judgment, including the adequacy of tissue oxygenation.

### Recombinant Human Erythropoietin Clinical Pharmacology

Because the erythropoietic response is blunted in patients with anemia of critical illness, pharmacological strategies that stimulate erythropoiesis are highly desirable. In the United States, two erythropoiesis-stimulating drugs are available: epoetin alfa and darbepoetin. To date, there are no published reports of using darbepoetin for the treatment of anemia of critical illness and, therefore, its use will not be discussed further.

Epoetin alfa is produced by recombinant DNA technology from Chinese hamster ovary cells. The resulting

Hebert PC, Wells G, Blajchman MA, et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. *N Engl J Med* 1999;340:409–17.

protein contains a polypeptide chain that consists of 165 amino acids with four glycosylation sites that contain oligosaccharide chains. The amino acid sequence of epoetin alfa is identical to that of endogenous EPO, but glycosylation differs so that the carbohydrate content (about 40%) is greater than endogenous EPO (about 30%). Clearance of epoetin alfa occurs through EPO receptor-mediated uptake. Therefore, clearance of epoetin alfa is a saturable process, dependent on the availability of EPO receptors. Indeed, epoetin alfa exhibits nonlinear pharmacokinetics, with increasing doses associated with decreased clearance, increased elimination half-life, and prolonged duration of activity. For example, the area under the curve for fixed-dose epoetin alfa (40,000 IU) given once weekly is almost 4-fold higher than 3 times/week dosing (150 IU/kg/dose), considerably greater than the differences in the cumulative weekly doses. This decreased clearance with higher doses has potential implications in the discussion that follows regarding the use of epoetin alfa in critically ill patients with anemia.

### Use in Anemia of Critical Illness

Like endogenous EPO, epoetin alfa stimulates erythropoiesis in a dose-dependent manner. Epoetin alfa is used primarily in treating anemia in patients with end-stage renal disease undergoing hemodialysis, anemia in patients with the human immunodeficiency virus treated with zidovudine, and anemia secondary to cancer chemotherapy. Epoetin alfa can also reduce the need for allogenic blood transfusions in perioperative patients undergoing elective, noncardiac, nonvascular procedures who are at increased risk of significant blood loss. Although the use of epoetin alfa in this setting may be relevant to clinical pharmacists caring for patients in the surgical ICU, the role of epoetin alfa in preventing perioperative blood transfusions is not the focus of this chapter and is not discussed further.

Given the pathophysiology of anemia of critical illness (blunted EPO response secondary to inflammation), the use of epoetin alfa to treat anemia of critical illness has generated considerable excitement and debate. Epoetin alfa has been shown to reverse the inhibition of erythropoiesis in patients with chronic inflammation such as anemia of chronic disease and rheumatoid arthritis. Therefore, the use of epoetin alfa in the treatment of anemia of critical illness seems rather intuitive and has been studied in recent years. The rationale for using epoetin alfa in this setting is 4-fold: 1) inflammation is present in many critically ill patients contributing to the development of anemia; 2) epoetin alfa has been shown to overcome the blunted erythropoietic response in chronic inflammatory states, and its use in critically ill patients may be effective in treating or preventing anemia of critical illness; 3) the need for allogenic blood transfusions as a result of anemia may be decreased by treating or preventing anemia; and 4) epoetin

alfa may decrease morbidity and mortality that results from impaired tissue oxygenation by treating or preventing anemia.

The first study to investigate the use of epoetin alfa in critically ill patients with anemia was conducted in 40 burn patients with burns over about 40% of their body surface area. Nineteen patients received epoetin alfa; the remainder received placebo. Epoetin alfa was initiated within 72 hours of admission and given subcutaneously at a dose of 300 IU/kg/day for 7 days, followed by 150 IU/kg every other day. Total duration of epoetin alfa therapy was 30 days. Thereafter, epoetin alfa could be continued in a nonblinded fashion at a dose of 150 IU/kg 3 times/week. Epoetin alfa failed to demonstrate a benefit over placebo in terms of reducing the total volume of transfused blood, improving hematologic indices, or correcting iron studies. However, erythropoiesis in both groups may have been hindered by the lack of iron supplementation, as only 13 patients (eight in the epoetin group, five in the placebo group) received iron supplementation (oral ferrous sulfate).

In contrast, a small study of 19 patients with major trauma or abdominal surgery and evidence of multiorgan failure demonstrated that epoetin alfa increased reticulocyte counts. Nine patients were given epoetin alfa 600 IU/kg intravenously 3 times/week for 3 weeks. The remaining patients received placebo (saline). All patients were treated with iron supplementation (intravenous ferric chloride in addition to elemental iron supplementation in their enteral feeds) and weekly supplementation with intravenous folate and cyanocobalamin. Increases in reticulocyte counts compared with baseline reached statistical significance at weeks 2 and 3 in the epoetin alfa group; between-group differences were statistically significant at week 3. Excluding patients with evidence of major bleeding, fewer patients in the epoetin alfa group (29%) required blood transfusions than in the placebo group (60%), although this difference did not reach statistical significance.

Similar results were reported in a series of 36 critically ill patients with anemia. Patients were randomized to one of three groups: intravenous folic acid 1 mg/day; intravenous folate plus intravenous iron saccharate 20 mg/day; or intravenous folate, intravenous iron, and epoetin alfa 300 IU/kg subcutaneously on days 1, 3, 5, 7, and 9. Hematologic studies demonstrated that erythropoiesis was enhanced only in the triple therapy group as evidenced by statistically significant increases in both reticulocyte count and concentration of transferrin receptors. Reticulocyte counts in the triple therapy group were higher than in the other two groups beginning on day 8 and continuing through day 15. Compared with the folate-only group, the mean number of transfused units of blood were lower in patients in the folate-iron group and in patients in the folate-iron-epoetin alfa group ( $12 \pm 14$ ,  $5 \pm 7$ ,  $7 \pm 7$  in the three groups, respectively; no p value was reported).

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Still JM, Belcher K, Law EJ, et al. A double-blinded prospective evaluation of recombinant human erythropoietin in acutely burned patients. *J Trauma* 1995;38:233-6.

Gabriel A, Kozek S, Chiari A, et al. High-dose recombinant human erythropoietin stimulates reticulocyte production in patients with multiple organ dysfunction syndrome. *J Trauma* 1998;44:361-7.

van Iperen CE, Gaillard CAJM, Kraaijenhagen RJ, Braam BG, Marx JJM, van de Wiel A. Response of erythropoiesis and iron metabolism to recombinant human erythropoietin in ICU patients. *Crit Care Med* 2000;28:2773-8.

**Table 1-1. Eligibility Criteria for the Participation in the EPO Critical Care Trial**

Inclusion Criteria	Exclusion Criteria
Intensive care unit length of stay = 3 days	Renal failure requiring hemodialysis
Age older than 18 years	Uncontrolled hypertension
Hematocrit < 38%	New onset or uncontrolled seizures
Provision of informed consent	Acute burns
	Pregnancy or lactation
	Acute ischemic heart disease
	Acute gastrointestinal bleeding
	Prior treatment with epoetin alfa
	Participation in another research protocol
	Anticipated discharge from intensive care unit within 2 days of screening (total intensive care unit length of stay < 5 days)

EPO = erythropoietin.

Encouraged by the increased erythropoiesis reported in these studies and the trend toward decreased need for blood products in critically ill patients treated with epoetin alfa, two large-scale studies have been conducted to formally investigate the effect of epoetin alfa on transfusion of blood products in this setting. The first study assessed whether the routine use of epoetin alfa in critically ill patients with anemia decreased the total number of units of blood transfused in the ICU. In this trial, 160 patients were randomized to receive either epoetin alfa 300 IU/kg/day subcutaneously beginning on day 3 of admission to the ICU and continuing through day 7 (thereafter receiving injections every other day for up to 6 weeks) or matching placebo. Patients also received iron supplementation (oral or intravenous for patients unable to take oral iron or those demonstrating an inadequate response to oral iron). Patients in the epoetin alfa group received a mean of  $8.3 \pm 4.5$  doses ( $23,000 \pm 7000$  units/dose). The cumulative number of units of RBCs transfused was reduced by 45% in the epoetin alfa group (166 units in patients treated with epoetin alfa vs. 305 units in the placebo group;  $p < 0.002$ ). A trend toward fewer patients requiring blood transfusions or dying between day 8 and day 42 was also demonstrated in the epoetin alfa group (45% in the epoetin alfa group vs. 55% in the placebo group; relative risk = 0.8; 95% confidence interval [CI] 0.6–1.1). Reticulocyte counts, hematocrit change from baseline, and final hematocrit were all significantly greater in patients treated with epoetin alfa.

Although the findings from this study were encouraging, total enrollment (160 patients) was insufficient to meet the *a priori* power calculations (206 patients required for 80% power); enrollment was halted due to slow recruitment. In addition, of the 1778 patients screened for enrollment, only 329 (19%) met inclusion and exclusion criteria, and fewer than 50% of these patients were enrolled. Therefore, the

results of this study may not be generalizable to a vast majority of critically ill patients.

Given the impressive reduction in blood products transfused found in the previous study, the same group of authors (EPO Critical Care Trials Group) conducted a similar, but larger, placebo-controlled study to investigate whether epoetin alfa would decrease the number of critically ill patients requiring a blood transfusion. The major difference from the preceding study was the dose of epoetin alfa used. Given the pharmacokinetic advantages of using high, intermittent doses of epoetin alfa described earlier, this study used a fixed-dose of epoetin alfa 40,000 IU subcutaneously once weekly for up to four doses. Like previous studies, epoetin alfa was held if, at the time of injection, the pre-dose hematocrit was greater than 38%. In addition, eligibility criteria were liberalized somewhat to be more inclusive (Table 1-1). A total of 1302 patients were randomized to receive either epoetin alfa or placebo. The relative risk of receiving a blood transfusion was reduced by more than 30% compared with placebo [50.5% vs. 60.4%;  $p < 0.001$ ; odds ratio (OR) = 0.67; 95% CI = 0.54–0.83]. Similarly, the cumulative number of units transfused per patient was lower in the epoetin alfa group. Mortality rates were not affected by treatment assignment (14% vs. 15% in the epoetin alfa and placebo groups, respectively). Similarly, length of hospital stay and ICU-free days did not differ between the groups. However, there was a trend toward decreased need for readmission to the ICU in patients treated with epoetin alfa compared with placebo (9.8% vs. 13.3%, respectively;  $p = 0.07$ ). Fewer patients required mechanical ventilation and reventilation in the epoetin alfa groups; however, neither of these differences was statistically significant.

This study confirms what was demonstrated in the earlier study: the use of epoetin alfa in critically ill patients with anemia decreases the need for blood transfusion. However, epoetin alfa did not appear to affect the clinical sequelae of anemia in these patients. Mortality, the need for mechanical ventilation, and length of stay, both in the ICU and overall, were unchanged. In addition, although more than 33,000 critically ill patients were screened for eligibility, fewer than 30% of patients screened were eligible for the trial and only 4% were actually included in this analysis. Therefore, external validity of these results may be limited.

### Adverse Events

Epoetin alfa is generally well-tolerated. In anemic patients treated with epoetin alfa chronically (e.g., patients on hemodialysis), adverse events of concern include the development or worsening of hypertension, seizures, and thrombotic events. However, with short-term use (e.g., surgical patients), adverse events occurring more frequently than placebo were relatively benign, including skin/injection site reactions, pruritus, vomiting, dyspepsia, and edema. There have been some reports of deep vein thrombosis, but it is difficult to ascertain causality given the

Corwin HL, Gettinger A, Rodriguez RM, et al. Efficacy of recombinant human erythropoietin in the critically ill patient: a randomized, double-blind, placebo-controlled trial. *Crit Care Med* 1999;27:2346–50.

Corwin HL, Gettinger A, Pearl RG, et al. Efficacy of recombinant human erythropoietin in critically ill patients: a randomized controlled trial. *JAMA* 2002;288:2827–35.

low event rates in these studies and the fact that thromboembolic risk is high in the postoperative setting.

In the larger studies investigating the use of epoetin alfa in critically ill patients, the rates of adverse events and serious adverse events were not statistically different from patients receiving a placebo. Both thrombocytopenia and thrombocytosis were more common, albeit rare, in patients treated with epoetin alfa. However, platelet or other blood or clotting disorders occurred in only 2% of patients in the latest study and the incidence was not different between groups. Therefore, short-term use of epoetin alfa in critically ill patients appears to be well-tolerated; the incidence of serious adverse events in this setting is comparable with placebo.

### Role of the Pharmacist

The pharmacist can play an important role in determining the appropriate use of epoetin alfa in the critical care setting. First, patient selection is important. As stated above, the external validity of the largest two studies is limited. In each study, patients with acute ischemic heart disease, gastrointestinal tract bleed, renal failure requiring hemodialysis, and uncontrolled hypertension were excluded. Therefore, the safety and efficacy of epoetin alfa in critically ill patients with these comorbidities is unknown, and its use may not be appropriate in these patients. The time course of response to epoetin alfa should also be considered. Increases in erythropoiesis (increased reticulocyte counts) may not occur until the second or third week of therapy. Therefore, patients anticipated to have relatively brief stays in the ICU may not derive much benefit from epoetin alfa.

Pharmacists undoubtedly play a role in determining the most effective and efficient dosing regimen of epoetin alfa in the ICU setting. It would appear that 40,000 IU subcutaneously once weekly for up to four total doses is the most effective dose of epoetin alfa. Therefore, in the interest of cost-effective medicine, pharmacists should assure that excessive doses (greater than 40,000 IU/week) are avoided. In addition, because the duration of epoetin alfa therapy in most of the studies investigating its use in anemia of critical illness was 3 weeks or less, the safety, efficacy, and cost-effectiveness of extended courses of epoetin alfa (longer than 3 weeks) are not known. Most of the studies had provisions for holding epoetin alfa if the hematocrit exceeded 38%. Consequently, pharmacists should monitor pre-dose hematocrit values and withhold therapy in patients above this threshold, decreasing unnecessary doses and inappropriate use of resources. Finally, pharmacists should assess the iron studies of patients with anemia of critical illness and initiate iron supplementation (discussed below) in appropriate patients to promote an optimal erythropoietic response to epoetin alfa.

## Iron Supplementation

### Oral Iron Supplements

Iron is required for adequate erythropoiesis to ensue. Given that patients with anemia of critical illness often have either relative or overt iron deficiency, iron supplementation is important to optimize erythropoiesis. Oral iron supplementation is the most convenient, safest administration route. No studies have investigated oral iron supplementation alone in the treatment of anemia of critical illness. However, oral iron has been studied as a treatment for anemia in patients undergoing open heart surgery and was not found to be effective. Oral absorption of iron in the critical care setting may be impaired, perhaps explaining the lack of benefit seen in open heart surgery. In addition, oral iron interacts with several drugs by binding them within the gastrointestinal tract. Therefore, the absorption of drugs such as quinolone antibiotic drugs and phenytoin, drugs frequently administered in this setting, may be decreased when administered concomitantly with oral iron, limiting their effectiveness as well. Consequently, the use of oral supplementation to treat anemia of critical illness is limited, at best. Given the limitations of oral supplementation, parenteral iron supplementation may be considered in patients with anemia of critical illness.

### Parenteral Iron Supplements

Intravenous iron supplementation is often considered in patients with iron deficiency where the gastrointestinal tract cannot be used, when absorption from the gastrointestinal tract is questionable, or who have demonstrated an inadequate response to oral iron supplementation. Several studies have shown that parenteral iron potentiates the erythropoietic effect of epoetin alfa. In a small study, seven patients were given intravenous iron sucrose 200 mg following epoetin alfa 300 IU/kg intravenously and compared to seven patients receiving epoetin alfa alone. Patients given epoetin alfa alone had a marked reduction in ferritin, whereas patients receiving both iron and epoetin alfa maintained their ferritin levels, preserving iron stores in the face of increased erythropoiesis. Intravenous iron dextran, given either as a bolus injection or total dose infusion, was superior to both no iron and oral iron in 157 cancer patients with chemotherapy-induced anemia receiving weekly subcutaneous injections of epoetin alfa. Two-thirds of the patients given iron dextran demonstrated a hematopoietic response compared with 36% in the oral iron group and only 25% in the no iron group.

The only study comparing the use of parenteral iron to control in the setting of anemia of critical illness was discussed previously. To summarize, in the absence of concomitant epoetin alfa, the combination intravenous iron saccharate 20 mg plus folate produced an inferior erythropoietic response in 36 critically ill patients with anemia. However, the number of blood products transfused was similar between these two groups and lower compared with patients given intravenous folate alone. Most of the

Major A, Mathez-Loic F, Rohling R, Gautschi K, Brugnara C. The effect of intravenous iron on the reticulocyte response to recombinant human erythropoietin. *Br J Haematol* 1997;98:292-4.

Auerbach M, Ballard H, Trout JR, et al. Intravenous iron optimizes the response to recombinant human erythropoietin in cancer patients with chemotherapy-related anemia: a multicenter, open-label, randomized trial. *J Clin Oncol* 2004;22:1301-7.

other trials investigating the effect of epoetin alfa mandated the use of either oral or intravenous iron supplementation in all patients. Therefore, one cannot determine the effect parenteral iron had on erythropoiesis in these studies, given the lack of a control group.

Although studies investigating the use of parenteral iron for anemia of critical illness are lacking, intravenous iron preparations have been investigated in anemia associated with other inflammatory states. One analysis randomized 40 patients with Crohn's disease to receive iron saccharate 200 mg intravenously alone or in combination with epoetin alfa 150 IU/kg subcutaneously 3 times/week. Seventy-five percent of patients in the iron saccharate group had an acceptable erythropoietic response (increase in hemoglobin greater than 2 g/dL from baseline) compared with 95% in the combination group; this difference was not statistically significant. The maximum hemoglobin achieved and magnitude of change were significantly greater in patients receiving the combination of intravenous iron and epoetin alfa. Similarly, 60 postpartum women were randomized to receive either intravenous iron sucrose 200 mg alone, iron sucrose in combination with epoetin alfa 300 IU/kg/day for 4 days, or the combination of oral iron and folate. Patients treated with both intravenous iron and epoetin alfa achieved higher hematocrit values at days 7 and 14 and were more likely to achieve the predefined goal hematocrit at each time period compared with either of the other two groups.

Despite the paucity of data in patients with anemia of critical illness, studies of anemia in other settings support that iron supplementation potentiates the erythropoietic effect of epoetin alfa. It appears that intravenous supplementation is more effective in this regard than oral iron. Although somewhat controversial, there is concern that administering iron to critically ill patients may result in oxidative stress, potentially impairing several biologic processes, including the ability to fight infection. As a result, in critically ill patients treated with iron supplementation, it is advisable to monitor iron indices regularly to avoid iron overload and the toxicities described above.

In the United States, three parenteral iron formulations are available: iron dextran, iron sucrose, and ferric gluconate. Each preparation is associated with a fairly high incidence of adverse effects. Hypersensitivity reactions have been reported with all injectable formulations of iron, but the incidence of severe or life-threatening reactions is generally thought to be higher with iron dextran. Therefore, many clinicians may opt to use a parenteral iron formulation other than iron dextran.

### **Hemostatic Drugs**

Because active bleeding contributes to the development of anemia in many critically ill patients, pharmacological strategies to induce hemostasis may be necessary. These drugs are commonly used either to reverse iatrogenic coagulopathies secondary to toxicity from antithrombotic

drugs or to rapidly achieve hemostasis in a patient with massive hemorrhaging, often following surgical procedures.

### **Reversal of Drug-Induced Coagulopathies**

Iatrogenic coagulopathy secondary to excessive warfarin dosing can contribute to anemia in critically ill patients. Reversal of this type of coagulopathy can be challenging and, if bleeding is also present, requires the administration of intravenous vitamin K to reverse warfarin's antagonistic effects on clotting factors II, VII, IX, and X. Fresh frozen plasma (FFP) may also be warranted to expedite the reversal and essentially replenish the patient with the activated clotting factors depleted during warfarin therapy. Recombinant activated factor VII (rFVIIa) is a new product to the critical care market, which has shown some benefit in the reversal of warfarin toxicity. A more extensive discussion of the potential role of this product can be found later in this chapter.

The treatment of coagulopathies caused by antiplatelet agents is more troublesome, particularly in the perioperative setting. Although some surgeons are comfortable operating on patients treated with aspirin, platelet transfusions appear to be beneficial for those with excessive hemorrhaging in managing this coagulopathy. For patients treated with the adenosine diphosphate receptor antagonists, ticlopidine or clopidogrel, management of coagulopathy can be difficult. Although many drugs have been investigated, no known antidotes exist for this class of platelet inhibitors. Platelet transfusions are usually attempted, but with little efficacy. Platelet dysfunction secondary to these drugs may persist up to 7 days, the time necessary to produce new platelets.

### **Treatment of Bleeding**

#### ***Antifibrinolytic Drugs***

To limit blood loss from hemorrhagic sources in ICU patients, clinicians can choose from many pharmacological interventions. The underlying pathology of the patient's disease and the mechanism of the hemostatic drug will determine the most appropriate intervention. Ultimately, these compounds act to stabilize existing clots (e.g., antifibrinolytic drugs), improve the functionality of platelet adherence (e.g., desmopressin), or activate the clotting cascade (e.g., rFVIIa.)

The fibrinolytic system is mediated by the conversion of plasminogen to plasmin. Once plasmin is formed, this compound breaks down fibrin, thus destroying fibrin clots that are responsible for hemostasis. The antifibrinolytic drugs, aminocaproic acid and tranexamic acid, are synthetic lysine analogs that antagonize the conversion of plasminogen to plasmin. The endogenous fibrinolytic system is rendered incapable of degrading fibrin, which stabilizes the fibrin clot. Tranexamic acid is reported to be 6–10 times more potent than aminocaproic acid in this respect. Another antifibrinolytic drug used in clinical practice is aprotinin. Aprotinin is a serine protease inhibitor that inactivates plasmin, inhibiting the fibrinolytic system

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Gasche C, Dejaco C, Waldhoe T, et al. Intravenous iron and erythropoietin for anemia associated with Crohn's disease: a randomized, controlled trial. *Ann Intern Med* 1997;126:782–7.

Breyman C, Richter C, Huttner C, Huch R, Huch A. Effectiveness of recombinant erythropoietin and iron sucrose vs. iron therapy only, in patients with postpartum anemia and blunted erythropoiesis. *Eur J Clin Invest* 2000;30:154–61.

and stabilizing fibrin.

The antifibrinolytic drugs have been studied extensively for the reduction of blood loss in the perioperative setting, primarily in patients undergoing cardiovascular, liver, and orthopedic surgeries. These studies have generated conflicting results and considerable controversy in recent years. For example, in 1999, a large meta-analysis compared the efficacy of all three drugs in 8409 patients undergoing cardiac surgery. This analysis evaluated not only the need for blood transfusions, but also the need for re-thoracotomy, mortality, and adverse effects. In the meta-analysis, aprotinin showed a 2-fold decrease in mortality compared with placebo. Also, significantly fewer patients treated with aprotinin required blood transfusions compared with placebo (42.5% vs. 62.7%, respectively; odds ratio [OR] = 0.37; 95% CI = 0.32–0.42). Compared with placebo, the lysine analogs decreased the need for blood transfusions by more than 50% (OR = 0.46; 95% CI = 0.34–0.64) and there was a trend toward lower mortality; however, this difference was not statistically significant (OR = 0.78; 95% CI = 0.27–2.16). In contrast, two recent analyses challenge the safety of aprotinin relative to the lysine analogues. A case-controlled comparison of aprotinin and tranexamic acid in 998 cardiac surgery patients found the rate of postoperative renal dysfunction to be 40% higher in patients treated with aprotinin compared with those given tranexamic acid. An observational study of 4374 cardiac surgery patients found the risk of aprotinin-related adverse events to be even greater. Aprotinin was associated with a more than 2-fold increased risk of renal adverse events, including the need for hemodialysis, and an almost 50% increase in the composite of renal, cardiovascular, and cerebrovascular ischemic events. Although these data are not derived from randomized, controlled, clinical trials, many institutions have suspended the use of aprotinin until additional studies are performed.

Although the data are not as extensive as in cardiac surgery, these drugs have shown promise at reducing blood loss and reducing the need for transfusions in patients undergoing orthopedic and transplant surgery. However, reports are conflicting regarding efficacy in these settings, and the timing of administering the antifibrinolytic drugs appears to play a role. Until further research is conducted in settings other than cardiovascular surgery, antifibrinolytic drugs should be used with caution for bleeding unrelated to cardiovascular surgery.

### ***Desmopressin***

Desmopressin is a commercially available analog of arginine vasopressin, which is widely used in the management of diabetes insipidus. The compound also contains *in vivo* properties that prompted further investigation as a hemostatic agent. Desmopressin has the ability to stimulate the endothelial tissue to release

von Willebrand factor and factor VIII. This mechanism is significant because both von Willebrand factor and factor VIII play a role in improving platelet function. In addition, the ability to stimulate release of VIII and von Willebrand factor make the drug useful for managing some forms of hemophilia A and von Willebrand's disease type I.

Desmopressin may also have a role in patients without hemophilia treated in the ICU. Because uremia causes platelet dysfunction, it may be especially useful in managing and preventing uremic bleeding. The desmopressin dose for managing uremic bleeding ranges from 0.3 mcg/kg to 0.4 mcg/kg administered intravenously over 30 minutes. Of note, tachyphylaxis is often encountered with desmopressin. Therefore, administering additional doses is unlikely to provide clinical benefit. In terms of adverse effects, some patients may experience flushing, headache, and dizziness. Hyponatremia is also a concern because desmopressin increases the reabsorption of free water in the collecting ducts of the kidney. Thrombotic complications, namely myocardial infarction, have been observed with the administration of desmopressin. Because of this adverse effect and the failure to reduce the need for blood transfusions in published studies, desmopressin should not be used to control hemorrhage during or before cardiac surgery or in patients with significant cardiac disease.

### ***Recombinant Activated Factor VII***

Recombinant activated factor VII is the newest, and perhaps the most promising, hemostatic drug developed. This product is approved for the treatment of hemophilia in patients with inhibitors of factor VIII and IX. In the extrinsic pathway of the clotting cascade, the first step in activation of the coagulation system is the release of tissue factor at the site of endothelial injury. Activated factor VII (factor VIIa) and tissue factor form a complex that activates factor IX and factor X. Under normal circumstances, low levels of factor VIIa are found in the circulation, which may be insufficient to achieve hemostasis in the event of acute, severe vascular injury. Administration of rFVIIa provides sufficient concentrations of factor VIIa to the injury site, which, in theory, promotes local initiation of the coagulation cascade while avoiding systemic activation of the clotting cascade and subsequent thromboembolic events.

Initially, several case reports and small case series in trauma patients without hemophilia but with severe bleeding suggested that rFVIIa administration promptly achieved hemostasis and decreased the need for blood product administration (packed RBCs and FFP). Subsequently, larger case series and small clinical trials demonstrated similar results in a wide variety of patient populations, including reversal of warfarin toxicity in neurosurgical patients, hemorrhagic stroke, and catastrophic bleeding following solid organ transplantation, cardiac surgery, orthopedic surgery, and trauma.

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Levi M, Cromheecke ME, de Jonge E, et al. Pharmacological strategies to decrease excessive blood loss in cardiac surgery: a meta-analysis of clinically relevant endpoints. *Lancet* 1999;354:1940–47.

Karkouti K, Beattie WS, Dattilo KM, et al. A propensity score case-control comparison of aprotinin and tranexamic acid in high-transfusion-risk cardiac surgery. *Transfusion* 2006;46:327–38.

Mangano DT, Tudor IC, Dietzel C for the Multicenter Study of Perioperative Ischemia Research Group and the Ischemia Research and Education Foundation. The risk associated with aprotinin in cardiac surgery. *N Engl J Med* 2006;354:353–65.

**Table 1-2. Comparative Costs of Therapies Used to Treat Anemia of Critical Illness**

Treatment	Dose	Cost Per Dose
Packed RBC	Unit	\$191–\$391 <sup>a</sup>
Epoetin alfa	40,000 IU	\$570
Iron		
Oral iron (ferrous sulfate)	325 mg TID	< \$1
Iron dextran	1000 mg	\$377
Iron sucrose	200 mg	\$138
Ferric gluconate	125 mg	\$86
Antifibrinolytics		
Aprotinin	280 mg	\$543
Aminocaproic acid (IV)	10 g	\$37
Tranexamic acid (IV)	1000 mg	\$36
Desmopressin	20 mcg	\$17
Recombinant activated factor VII	1.2 mg	\$1776

<sup>a</sup>Costs (2001 dollars) derived from Participants of the Cost of Blood Consensus Conference. The cost of blood: multidisciplinary consensus conference for a standard methodology. *Transfus Med Rev* 2005;19:66–78. Doses are based on a 70-kg patient requiring an increase in hemoglobin of 2 g/dL. Costs presented in US dollars, derived from the average wholesale price published in Medical Economics Co. 2005 Drug Topics Red Book. Montvale, NJ: Medical Economics Co., 2005. IV = intravenous; RBC = red blood cell; TID = 3 times/day.

Many controversies exist regarding the use of rFVIIa in patients without hemophilia. First, the effective dose for patients without hemophilia is unknown. Many case reports used doses similar to the approved dose for hemophilia (90 mcg/kg administered every 2–3 hours). However, others have reported lower doses may be as safe and effective. In fact, administration of as little as 1.2 mg, or one vial, of rFVIIa may be effective. Because rFVIIa has a short half-life, it must be administered frequently in patients with hemophilia. However, in patients without hemophilia, it is unknown whether repeated dosing of rFVIIa is necessary.

Adverse effects, in particular thrombosis, are another major concern with the use of rFVIIa because of its potency as a hemostatic drug. From the currently available evidence in patients without hemophilia, the risk of thromboembolic events are relatively low following rFVIIa administration. Anecdotally, administering large doses of rFVIIa via continuous infusions appears to be associated with a higher risk of thrombosis.

Lastly, cost is a major concern surrounding the use of rFVIIa in patients without hemophilia. Acquisition cost of this product is very high (Table 1-2). If hemophilia doses are used (90 mcg/kg), the acquisition cost of rFVIIa for a 70-kg patient may be as high as \$10,000 for a single dose (5–6 vials). Until the results from dose-finding studies are completed, the safety and efficacy of rFVIIa in patients without hemophilia remain unknown, clouding the pharmacoeconomic picture.

A guideline from the Washington University School of Medicine/Barnes Jewish Hospital offers suggestions as to the appropriate use of rFVIIa. Although other consensus

guidelines for the use of rFVIIa exist (e.g., University HealthSystem Consortium/Society of Blood Management), the Washington University School of Medicine guideline provides clinicians with more specific recommendations regarding rFVIIa use in various clinical settings. Of more importance, the guideline warns against the inappropriate use of rFVIIa in patients who have known hypercoagulability, excessive bleeding during disseminated intravascular coagulation, or other disease states associated with generalized activation of the hemostatic system. Until more is known about appropriate dosing and the dose-adverse effect relationship, rFVIIa should be reserved for life-threatening hemorrhagic events in patients without hemophilia. Because of the short half-life, rFVIIa should always be administered in conjunction with FFP and potentially vitamin K when reversing bleeding in patients without hemophilia. In addition, it may be necessary to redose rFVIIa to achieve the appropriate level of hemostasis.

Given the controversies surrounding the use of rFVIIa, pharmacists should play a role in determining the appropriateness of this drug's use and avoiding its inappropriate use. Although the most effective dose of rFVIIa in patients without hemophilia is unknown in this setting, pharmacists should be aware of the doses studied, the potential need to redose, and the need to administer FFP and other reversal agents (e.g., vitamin K).

### Pharmacoeconomic Considerations

Formal pharmacoeconomic analyses of the various treatment strategies for anemia of critical illness are, for the most part, lacking. Because the costs associated with many of the therapies discussed above are quite high (Table 1-2), one has to compare the cost of care in the context of the benefit gained. In the case of iron supplementation and epoetin alfa, the costs associated with these treatments must be compared with the benefit of reduced need for transfusions. For the hemostatic drugs, the costs associated with these therapies must be weighed against the costs and complications associated with not only blood product administration, but also surgical exploration or re-exploration that may be necessary to achieve hemostasis.

Presently, administration of blood products remains the standard of care in the management of anemia of critical illness. However, like other therapies used to treat anemia of critical illness, the costs associated with the administration of blood products are considerable. To accurately represent the total costs associated with the use of blood products, several elements must be included in the cost estimate, including but not limited to the following: donor recruitment and qualification; blood collection, processing, and screening; blood destruction, donor notification, and tracking; blood inventory, storage, and transport; and transfusion-related costs (preparation, administration, and follow-up). Including these and other costs, the estimated cost per unit of blood administered has been estimated

Goodnough LT, Lubin DM, Zhang L, et al. Transfusion medicine service policies for recombinant factor VIIa administration. *Transfusion* 2004;44:1325–31.

Participants of the Cost of Blood Consensus Conference. The cost of blood: multidisciplinary consensus conference for a standard methodology. *Transfus Med Rev* 2005;19:66–78.



**Table 1-3. Blood Conservation Strategies in Critically Ill Patients**

Strategies to Prevent Blood Loss	Strategies to Decrease Administration of Blood Products
Use of pediatric-sized blood collection tubes	Adoption of restrictive transfusion practices/thresholds
Use of venous arterial blood management protection systems	Epoetin alfa plus iron supplementation to promote erythropoiesis
Increased use of point-of-care testing in lieu of phlebotomy	Use of hemostatic drugs in patients with uncontrolled bleeding
Education	Education

between \$191 and \$391 (2001 dollars). Therefore, when evaluating the pharmacoeconomics of therapies, including drugs, associated with a reduction in the use of blood products, one must compare the total cost of administering blood products to the costs of these therapies.

Recently, two pharmacoeconomic analyses evaluated the use of epoetin alfa in critically ill patients with anemia. The first analysis evaluated the number-needed-to-treat and the cost necessary to prevent transfusion-related adverse events by treating critically ill patients with anemia with epoetin alfa. It was estimated that more than 5000 patients would need to receive epoetin alfa to prevent one transfusion-related event, and almost 30,000 would need to be treated to prevent a serious transfusion-related event. More than 80,000 would need to be treated to prevent a fatal transfusion-related adverse event. The estimated costs to prevent each event were \$4.7 million, \$25.6 million, and \$71.8 million, respectively. Critics of this analysis point toward the rarity of the transfusion-related adverse events selected for the analysis, suggesting that the outcomes are overstated as a result. In contrast, another study suggested that the cost-effectiveness of epoetin alfa was acceptable. In this analysis, a decision tree was constructed to evaluate the incremental cost and quality-adjusted life years gained by treating critically ill patients with epoetin alfa. From a societal perspective, the incremental cost of using epoetin alfa to reduce transfusion of RBCs was estimated to be \$1,400–\$1,900. This corresponded to an incremental cost-effectiveness ratio between \$34,000 and \$47,000 per quality-adjusted life year. Using \$50,000 per quality-adjusted life year as the threshold, epoetin alfa was deemed to be cost-effective 52% of the time in Monte Carlo simulations. Of note, epoetin alfa was cost-effective in this analysis only if one assumes that RBC transfusions are associated with nosocomial infections.

## Patient-Specific Treatment Strategies

Anemia in critically ill patients is generally multifactorial. Therefore, it is difficult, if not impossible, to apply one treatment strategy to all patients. Because the primary goal in treating anemia of critical illness is preservation of adequate tissue oxygenation, the acuity and complexity of treatment depends on the presence of tissue hypoxia and/or ischemia. For patients demonstrating evidence of inadequate tissue oxygenation, administering

blood products to immediately correct the anemia is indicated. Likewise, for patients with severe anemia (i.e., hemoglobin less than 7 g/dL), administering blood products may also be necessary to maintain adequate oxygenation and prevent end-organ damage.

In patients without severe anemia or evidence of tissue hypoxia, anemia may be managed more conservatively. Correction of any nutritional deficiencies and underlying conditions that may exacerbate anemia or precipitate tissue hypoxia is necessary. Supplementation with folic acid and cyanocobalamin may also be indicated. For patients with evidence of overt or relative iron deficiency, iron supplementation is critical for optimal erythropoiesis to occur. The formulation used depends on the patient's clinical status, but parenteral supplementation appears to be more effective at stimulating an erythropoietic response in this setting, particularly in patients with transferrin saturation less than 20% and ferritin less than 100 ng/mL. Lastly, once weekly administration of epoetin alfa may be indicated in critically ill patients who are anticipated to have a prolonged stay (longer than 4 days) in the ICU.

In patients with anemia due, in part, to hemorrhage, the use of hemostatic agents may be indicated in addition to the therapies discussed above. Reversal agents such as vitamin K may be considered in patients with bleeding complications related to administration of warfarin. Other drugs that may be considered include the antifibrinolytic drugs, desmopressin, and rFVIIa.

Finally, preventing anemia is a goal in all critically ill patients. Therefore, strategies to minimize unnecessary blood draws and increase the efficiency of phlebotomy should be used. Prophylactic therapies should also be used. For example, prophylaxis of deep vein thrombosis may negate the need for treatment doses of unfractionated heparin, low-molecular-weight heparin, and/or warfarin, ultimately decreasing the risk of bleeding from these antithrombotic drugs. Likewise, stress ulcer prophylaxis decreases the risk of gastrointestinal tract bleeding and subsequent anemia.

## Blood Conservation Strategies

In an effort to prevent anemia in critically ill patients and to reduce or prevent the administration of blood products to these patients, several blood conservation strategies may be used. (Table 1-3) The backbone of any blood conservation

Shermlock KM, Horn E, Lipsett PA, Pronovost PJ, Dorman T. Number needed to treat and cost of recombinant human erythropoietin to avoid one transfusion-related adverse event in critically ill patients. *Crit Care Med* 2005;33:497–503.

MacLaren R, Sullivan PW. Cost effectiveness of recombinant human erythropoietin for reducing red blood cell transfusions in critically ill patients. *Value Health* 2005;8:105–16.

strategy is education. Clinicians caring for critically ill patients should be educated on the incidence and complications associated with anemia of critical illness; iatrogenic causes of anemia such as phlebotomy; preventive measures that may be used; the comparative safety and efficacy of the various pharmacological treatment approaches; and appropriate triggers for blood transfusion to minimize the use of blood products. Adoption of a blood conservation strategy that emphasizes a restrictive transfusion policy has decreased the number of transfused units by about 20% overall and up to 45% in some patient care areas.

Minimization of blood loss is an important aspect of any blood conservation strategy. Fortunately, several strategies can be adopted to decrease blood loss due to phlebotomy. The use of pediatric-sized phlebotomy tubes in critically ill adults can reduce the total volume of phlebotomized blood by half. The use of venous arterial blood management protection systems can reduce the amount of blood discarded during phlebotomy. Increased use of point-of-care testing can also decrease the total amount of phlebotomized blood in critically ill patients as these devices typically require only small quantities (drops) of blood. Of more importance, unnecessary blood draws should be avoided in lieu of more efficient phlebotomy practices. Finally, in patients with evidence of hemorrhage, the use of pharmacological drugs to achieve hemostasis may be necessary to avoid invasive surgical procedures.

## Conclusion

Anemia is present or develops in as many as 75% of critically ill patients. The anemia that develops is often multifactorial. However, in a vast majority of patients, the anemia cannot be explained by obvious sources (e.g., preexisting anemia or acute blood loss). The etiology of anemia in these patients is inflammation that results in a blunted erythropoietic response. The anemia is often exacerbated by ongoing blood loss (phlebotomy or active bleeding), as well as by comorbid conditions such as coagulopathies and nutritional deficiencies. Persistent anemia can lead to impaired tissue oxygenation, tissue hypoxia, and eventually organ dysfunction and failure. As a result, critically ill patients with anemia are likely to receive blood products and have an increased risk of mortality.

Treatment of anemia of critical illness is directed at preserving tissue oxygenation, correcting severe anemia, and minimizing blood loss. Currently, guidelines for the management of anemia of critical illness do not exist. In the absence of consensus guidelines, administration of blood products remains the standard of care. However, given the risks associated with blood product administration and the intermittent shortages of blood supply, more attention is being focused on restrictive transfusion policies and pharmacologic strategies to prevent and treat anemia of critical illness. The use of epoetin alfa in conjunction with iron supplementation has consistently been shown to enhance erythropoiesis and decrease the need for blood transfusion. However, clinical outcomes such as need for mechanical ventilation, length of stay, and mortality are

unaffected by this treatment approach. In special circumstances, the use of hemostatic drugs may be necessary to rapidly achieve hemostasis in the hemorrhaging patient. More research is needed to fully understand the role of each of these drugs in treating anemia of critical illness. Given the limited data and significant cost associated with each of these pharmacological treatment approaches, the pharmacist plays a key role in determining the appropriate use of these drugs in treating critically ill patients with anemia.

## Annotated Bibliography

1. Rudis MI, Jacobi J, Hassan E, Dasta JF. Managing anemia in the critically ill patient. *Pharmacotherapy* 2004;24:229–47.

This is an excellent review on the topic of anemia of critical illness for ICU clinicians, particularly pharmacists. Although the epidemiology and pathophysiology of anemia of critical illness are discussed briefly, the clinical consequences of anemia of critical illness are discussed in greater detail. The most useful part of this review, particularly for pharmacists, is the detailed review of the pharmacotherapy, including an in-depth review of the literature supporting the use of iron therapy, blood products, and erythropoietic agents. The authors also discuss the investigational “blood substitutes” currently in development. Lastly, the review provides some perspective in terms of pharmacoeconomic considerations in the treatment of anemia of critical illness.

2. Scharte M, Fink MP. Red blood cell physiology in critical illness. *Crit Care Med* 2003;31(suppl):S651–7.

This review provides a comprehensive look at the pathophysiological aspects of anemia of critical illness. Although some of these concepts are discussed in the review by Rudis et al. (Reference 1), the multifaceted physiology of red blood cells is described in much greater detail. The discussions on erythropoietin expression, iron metabolism, and the role of inflammatory mediators are helpful in understanding both the physiology and treatment of anemia of critical illness. Other factors contributing to the development of anemia in this setting are discussed as well, including hemolysis and phlebotomy in critically ill patients.

3. McLellan SA, McClelland DBL, Walsh TS. Anaemia and red blood cell transfusion in the critically ill patient. *Blood Rev* 2003;17:195–208.

This review article nicely supplements the reviews listed above. Pathophysiology is briefly summarized, followed by in-depth discussion on the risks of anemia in these patients and appropriate transfusion triggers, with an emphasis on special populations to consider. The article ends with a brief section on the potential role of recombinant erythropoietin in this setting. Also helpful are the many tables provided that nicely summarize causes of anemia of critical illness, the impact of anemia on oxygen-carrying capacity, critical hemoglobin triggers, physiological parameters to assess tissue oxygenation in critically ill patients, and issues related to red blood cell storage. Finally, the article ends with two bulleted summary boxes, one discussing practice points or clinical pearls and the other suggesting future research endeavors to better understand how to manage critically ill patients with anemia.

4. Murphy MF, Wallington TB, Kelsey P, et al, for the British Committee for Standards in Haematology, Blood Transfusion Task Force. Guidelines for the Clinical Use of Red Cell Transfusions. *Br J Haematol* 2001;113:24–31.

In the absence of consensus guidelines for transfusion of blood products in the United States, this article succinctly summarizes the recommendations of the British Committee for Standards in Haematology regarding transfusion practices in the United Kingdom. The article contains a section describing what parameters to evaluate before deciding to administer blood products. In that section, the classification of hypovolemic shock due to blood loss and the estimated risks associated with the use of blood products are summarized in tables. The sections that follow provide general guidelines for the use of blood transfusions, transfusion guidelines for acute blood loss, and transfusion guidelines based on hemoglobin concentration, all summarized in bullet points. Germane to this chapter are sections discussing blood transfusions in patients with poor hemostasis, anemia of critical illness, and patients undergoing surgical procedures.

5. National Health and Medical Research Council and the Australian Society of Blood Transfusion. Clinical Practice Guidelines on the Use of Blood Components (Red Blood Cells, Platelets, Fresh Frozen Plasma, Cryoprecipitate). Commonwealth of Australia, 2002.

This document provides the Australian guidelines for transfusion of blood products. They were developed as a joint initiative between the National Health and Medical Research Council and the Australian Society of Blood Transfusion in cooperation with the Commonwealth Department of Health and Ageing, the Royal Australian College of Surgeons, the Australian and New Zealand College of Anaesthetists, and others. Although the document is lengthy (113 pages), the findings and recommendations are summarized concisely. The recommendations are briefly summarized first. What follows are expanded discussions supporting each of the recommendations for the use of blood products. There is also a section devoted to implementation and evaluation of transfusion guidelines to aid clinicians and institutions in these endeavors. There are several figures, tables, and appendices that nicely summarize the salient points.

# SELF-ASSESSMENT QUESTIONS

## Questions 1–3 pertain to the following case.

A.S. is a 67-year-old woman admitted to the medical intensive care unit (ICU) for treatment of pneumonia and exacerbation of her chronic obstructive pulmonary disease. She has been complaining of increasing shortness of breath for 2 weeks, which worsened suddenly in the past 8 hours. Her medical history is significant for coronary artery disease and hypertension. Her vital signs at the time of admission to the medical ICU are as follows: blood pressure 121/60 mm Hg, heart rate 66 beats/minute, respiratory rate 22 breaths/minute, temperature 38.0°C, and oxygen saturation 89% on room air. Over the next 48 hours her clinical condition deteriorates, which requires endotracheal intubation, and her hemoglobin has decreased from 9.7 g/dL on admission to 8.4 g/dL without any obvious sources of blood loss. Her stool is negative for occult blood, and there is no evidence of blood or coffee-ground emesis in her nasogastric tube suctioning. Her current drugs include metoprolol XL 50 mg/day, enalapril 20 mg 2 times/day, prednisone 40 mg/day, famotidine 20 mg 2 times/day, piperacillin/tazobactam 2.25 g every 6 hours, and normal saline 42 mL/hour continuously (total volume of crystalloids administered since admission is 2 L). Her physician suspects anemia of critical illness and consults with you, the pharmacist.

1. Assuming that A.S. has anemia of critical illness, which one of the following best describes the etiology of this illness?
  - A. Likely a stress-induced gastric ulcer.
  - B. Decreased erythropoiesis.
  - C. Hemolysis.
  - D. Hemodilution due to excessive hydration.
2. Which one of the following laboratory findings is most

consistent with the diagnosis of anemia of critical illness?

- A. Normal serum iron (Fe) level, normal total iron binding capacity (TIBC), normal ratio of Fe:TIBC, and increased ferritin level.
  - B. Low serum Fe level, normal TIBC, low ratio of Fe:TIBC, and low ferritin level.
  - C. Normal Fe level, low TIBC, normal ratio of Fe:TIBC, and low ferritin level.
  - D. Low Fe level, low TIBC, low ratio of Fe:TIBC, and increased ferritin level.
3. On hospital day 3, A.S. becomes hypotensive and tachycardic. Cardiac enzymes are sent and reveal the following: creatinine phosphokinase 1820 units/L, creatinine kinase MB fraction 16.9 ng/mL, and troponin I 3.1 ng/mL. Her hemoglobin continues to trend downward; today it is 7.9 g/dL. Which one of the following treatment approaches is most appropriate for the management of A.S.'s anemia at this time?
    - A. Transfuse red blood cells (RBCs) because she is showing signs of inadequate oxygen delivery.
    - B. Withhold administration of RBCs until hemoglobin decreases to less than 7 g/dL.
    - C. Initiate ferrous sulfate 325 mg 3 times/day to increase Fe stores.
    - D. Initiate epoetin alfa 50 units/kg subcutaneously 3 times/week in response to her impaired erythropoiesis.

## Questions 4 and 5 pertain to the following case.

A.H. is a 57-year-old man admitted to the cardiac ICU for treatment of a non-ST-segment-elevation myocardial infarction. About 5 hours ago, he had percutaneous coronary intervention with implantation of two paclitaxel-eluting intracoronary stents in his left anterior descending coronary artery. He now has an expanding

hematoma in his right groin. Aside from pain at the site of the hematoma, A.H. is otherwise asymptomatic. His current antithrombotic drug regimen includes unfractionated heparin 800 units/hour continuous infusion, eptifibatid 2 mcg/kg/minute continuous infusion, aspirin 325 mg/day, and clopidogrel 75 mg/day. His vital signs are blood pressure 101/63 mm Hg, heart rate 84 beats/minute, respiratory rate 18 breaths/minute, temperature 37.1°C. His hemoglobin has decreased from 14.3 g/dL on admission (yesterday) to 10.6 g/dL (present), and A.H.'s physician consults with you regarding the use of recombinant activated factor VII (rFVIIa) to achieve hemostasis, prevent worsening anemia, and conserve the use of blood products.

4. Which one of the following statements is most compelling reason to avoid rFVIIa in A.H.?
  - A. A.H. has no history of hemophilia.
  - B. It should be reserved for patients with a hemoglobin less than 10 g/dL.
  - C. It may induce a hypercoagulable state.
  - D. The cost is prohibitive.
5. Which one of the following blood conservation strategies is recommended in critically ill patients such as A.H. to prevent anemia of critical illness and minimize the use of blood products?
  - A. Establish automatic transfusion triggers when the hemoglobin falls below 10 g/dL in ICU patients.
  - B. Improve phlebotomy practices by decreasing unnecessary blood draws and using blood-sparing techniques and devices.
  - C. Initiate epoetin alfa 40,000 units/week subcutaneously for up to 3 weeks in critically ill patients with hemoglobin less than 12 g/dL.
  - D. Use autologous blood donation in critically ill patients to decrease transfusion of allogenic blood products.

**Questions 6 and 7 pertain to the following case.**

G.Z. is a 47-year-old man admitted to the cardiac ICU for treatment of ST segment-elevation myocardial infarction. His medical history is significant for hypertension, dyslipidemia, and alcohol abuse. In the emergency department, he was hypotensive and tachycardic (blood pressure 90/50 mm Hg, heart rate 106 beats/minute) and was, therefore, given several boluses of intravenous fluids (total volume of normal saline administered: 2000 mL). He was noted to have ST depression in leads II, III, and AVF; was given the presumptive diagnosis of unstable angina; and was taken emergently to the cardiac catheterization laboratory where he underwent percutaneous coronary intervention of his right coronary artery and had an sirolimus-eluting intracoronary stent placed. His current drugs include intravenous unfractionated heparin 700 units/hour, abciximab 10 mcg/minute intravenously, 0.9% sodium chloride 125 mL/hour intravenously, aspirin 325 mg/day (one dose given in the emergency department), clopidogrel 75 mg/day (one dose of 300 mg given in the cardiac catheterization laboratory), metoprolol 25 mg 2 times/day, and famotidine 40 mg/day. His vital signs are

stable: blood pressure 110/70 mm Hg and heart rate 68 beats/minute. His weight has increased 3 kg since admission (less than 24 hours). Repeat laboratory assessment reveals that his hemoglobin has decreased from 13.4 g/dL on admission to 11.1 g/dL after admission to the ICU. G.Z. denies coffee-ground emesis, hematochezia, or abdominal pain. His vascular access site in the groin is without evidence of hematoma. His activated partial thromboplastin time is 70 seconds (goal: 60–80 seconds).

6. Which one of the following complications is G.Z. at greatest risk for developing secondary to his anemia?
  - A. Cerebrovascular accident.
  - B. Myocardial infarction.
  - C. End-stage renal disease requiring hemodialysis.
  - D. Lactic acidosis.
7. Which one of the following treatment approaches is most appropriate for G.Z. at this time?
  - A. Aminocaproic acid 5 g over 1 hour followed by 1 g/hour until hemostasis is achieved.
  - B. Epoetin alfa 40,000 IU/week subcutaneously.
  - C. Ferrous sulfate 325 mg orally 3 times/day, folic acid 1 mg/day orally, and cyanocobalamin 250 mcg/day orally.
  - D. Decrease the volume of intravenous fluid resuscitation with normal saline.

**Questions 8–11 pertain to the following case.**

E.G. is a 63-year-old woman who had a coronary artery bypass graft surgery 3 days ago. Her postoperative course was complicated by acute renal insufficiency, acute decompensated heart failure, pneumonia, and now anemia. Her medical history includes coronary artery disease, hypertension, dyslipidemia, diabetes mellitus, a cerebrovascular accident and a history of alcohol abuse. Her current drugs include enteric-coated aspirin 325 mg/day, simvastatin 20 mg/day, lisinopril 5 mg/day, metoprolol 25 mg 2 times/day, furosemide 40 mg intravenously 3 times/day, cefuroxime 1.5 g intravenously 2 times/day, lactated Ringer's solution 42 mL/hour intravenously, continuous infusion insulin at 2 units/hour, heparin 5000 units subcutaneously 3 times/day, and lansoprazole 30 mg/day. Her vital signs are presently stable. On admission, her hemoglobin was 12.4 g/dL, and her hematocrit was 36.1%. Today (hospital day 5), her hemoglobin is 8.8 g/dL and her hematocrit is 26.8%; both have been trending downward since the day of surgery. Her daily chest tube output has averaged 250 mL/day of seroanguinous fluid.

8. Which one of the following best describes the etiology of anemia in E.G.?
  - A. She is experiencing a bleeding complication from her coronary artery bypass graft surgery.
  - B. As a result of the postoperative inflammatory response, she has an inadequate production of erythropoietin, impairing erythropoiesis and causing anemia of critical illness.

- C. Given her history of alcohol abuse, the etiology of her anemia is likely secondary to nutritional deficiencies in iron, vitamin B<sub>12</sub>, and folate.
  - D. The decrease in her hemoglobin is likely the result of hemodilution secondary to administration of large amounts of intravenous fluids; she may not have anemia at all.
9. Her physician wants to initiate epoetin alfa to manage her anemia of critical illness. Which one of the following statements is the best rationale supporting the use of epoetin alfa in patients with anemia of critical illness?
- A. Reverses the inflammatory processes.
  - B. Lowers mortality.
  - C. Decreases the need for and blood transfusions.
  - D. Decreases length of ICU stay.
10. E.G.'s physician questions you regarding once-weekly versus 3 times/week dosing of epoetin alfa in this setting. Which one of the following is the best justification to support once-weekly dosing of epoetin alfa over 3 times/week dosing?
- A. Fewer thromboembolic events.
  - B. Saturation of erythropoietin (EPO) is less likely to occur.
  - C. Cost-effectiveness is improved.
  - D. The area under the curve is higher.
11. In addition to considering the use of epoetin alfa, which one of the following strategies is most likely to be effective as a blood conservation strategy in E.G.?
- A. Stress-ulcer prophylaxis and early initiation of enteral nutrition.
  - B. Prophylaxis of deep vein thrombosis with either unfractionated heparin or low-molecular-weight heparin.
  - C. Limiting phlebotomy sampling to once per day.
  - D. Avoiding the use of blood products unless E.G.'s hemoglobin decreases to less than 7 g/dL.

**Questions 12–14 pertain to the following case.**

M.N. is a 61-year-old woman who is being treated for sepsis following coronary artery bypass graft surgery 1 month ago. Her postoperative course has been complicated by a sternal wound infection with methicillin-resistant *Staphylococcus aureus*, bacteremia with resistant *Pseudomonas aeruginosa*, and anemia. Her medical history includes coronary artery disease, hypertension, dyslipidemia, diabetes mellitus, and anemia. Her current drugs include enteric-coated aspirin 325 mg/day, gemfibrozil 600 mg 2 times/day, niacin 500 mg 2 times/day, metoprolol succinate 400 mg/day, continuous infusion insulin at 4 units/hour, piperacillin/tazobactam 3.75 g every 6 hours, amikacin 550 mg/day, vancomycin 1 g/day, epoetin alfa 40,000 IU/week subcutaneously, heparin 5000 units subcutaneously 3 times/day, and lansoprazole 30 mg/day. On admission, her hemoglobin was 9.6 g/dL, and her hematocrit was 31.1%. In response to downward trends in her hemoglobin, epoetin alfa was initiated at 40,000 IU/week subcutaneously 21 days ago.

However, she continues to require intermittent blood transfusions and has not demonstrated adequate hematopoiesis. Today, her hemoglobin is 8.6 g/dL, and her hematocrit is 26.2%. In addition, iron studies reveal the following: serum Fe concentration 26 mcg/dL (normal: 37–170 mcg/dL), total Fe-binding capacity 143 mg/dL (normal: 250–450 mg/dL), transferrin 100 mg/dL (normal: 200–400 mg/dL), and ferritin 376 ng/dL (normal: 18–340 ng/dL). She does not show any signs of active bleeding.

12. Which one of the following is the best assessment of M.N.'s laboratory results?
- A. Iron deficiency anemia.
  - B. Macrocytic anemia.
  - C. Anemia of critical illness.
  - D. Hemolytic anemia.
13. Which one of the following is the best recommendation to manage M.N.'s persistent anemia?
- A. Iron supplementation.
  - B. Administer tranexamic acid.
  - C. Increase the dose of epoetin alfa.
  - D. Transfuse packed RBCs as needed to maintain hemoglobin greater than 8 g/dL.
14. Which one of the following statements is the best recommendation for Fe supplementation in critically ill patients with anemia?
- A. Avoid Fe supplementation because of the increased risk of oxidative stress.
  - B. Oral Fe supplementation is as effective as intravenous formulations in treating anemia of critical illness and, therefore, is the preferred administration route.
  - C. Intravenous Fe supplementation, given concomitantly with epoetin alfa, may be more effective than intravenous Fe alone in critically ill patients with anemia.
  - D. Iron dextran is more effective in the treatment of anemia of critical illness and is, therefore, preferred over either ferric chloride or Fe sucrose in this setting.
15. From the pharmacist's perspective, which one of the following is the best intervention to prevent blood loss and limit the use of blood products in M.N.?
- A. Minimize the number of vancomycin and amikacin serum concentrations.
  - B. Avoid drugs requiring therapeutic drug monitoring.
  - C. Use pediatric-sized phlebotomy tubes.
  - D. Ensure restrictive transfusion practices are applied to this patient.

**Questions 16–18 pertain to the following case.**

A 52-year-old man is admitted to the neurosciences ICU with the initial diagnosis of subarachnoid hemorrhage. He was found in his house by a neighbor after not having answered his phone for 2 days. The patient's medical history is significant for diabetes, hypertension, and a myocardial infarction 4 years ago. On admission, a left middle cerebral artery aneurysm was diagnosed via cerebral

angiography and was intravascularly secured. His drugs during the first 24 hours of admission in the ICU include nimodipine 60 mg every 4 hours, famotidine 20 mg 2 times/day, sliding scale insulin, metoprolol 50 mg 2 times/day, and simvastatin 20 mg at bedtime. He is also receiving 175 mL/hour of normal saline as maintenance fluid, and his weight is increased by 3 kg. Before admission the patient was also treated with aspirin. On admission, the patient's hemoglobin was 13.5 g/dL and 1 day later was reported as 11.7 g/dL. Currently, his serum sodium is 135 mEq/L. All other clinical chemistries are within normal limits.

16. Assuming that the patient has no signs of frank hemorrhage, which one of the following best explains this patient's anemia?
  - A. Excessive phlebotomy.
  - B. Onset of Fe deficiency anemia.
  - C. Continuous bleeding at the aneurysm site.
  - D. Excessive hydration.
17. The neurosurgery resident is concerned about this decrease in hemoglobin and wants to start the patient on hemostatic therapy. Which one of the following statements is the best reason to avoid desmopressin in this patient?
  - A. The risk of hyponatremia.
  - B. The patient has signs of uremia.
  - C. The patient has a history of myocardial infarction.
  - D. The patient is not severely anemic.
18. On day 14 of the patient's ICU stay, the pharmacist evaluates the hemoglobin trends and notices decreasing hemoglobin concentrations over time. Which one of the following laboratory parameters would best explain whether the bone marrow is appropriately responding to the impending anemia?
  - A. Reticulocyte count.
  - B. Serum ferritin concentration.
  - C. Serum transferrin concentration.
  - D. Serum cobalamin concentration.

**Questions 19–21 pertain to the following case.**

E.T. is a 42-year-old man who is admitted to the medical ICU after being found unconscious in a local park. He was brought in by paramedics who state that he was found alongside many empty wine bottles. The patient's physical examination is negative for any gross injury, and he is admitted to the unit for observation and frequent neurological examinations. On admission his liver function tests were within the normal limits except his albumin, which was 2.4 g/dL. His hemoglobin concentration is reported as 10.9 g/dL, and his international normalized ratio is elevated at 1.5.

19. Which one of the following is the most appropriate intervention for treating this patient's coagulopathy?
  - A. Recombinant activated factor VII.
  - B. Vitamin K 10 mg for three doses.
  - C. Fresh frozen plasma.
  - D. Cryoprecipitate.

20. Which one of the following laboratory parameters is the most useful for classifying this patient's type of anemia?
  - A. Mean corpuscular volume.
  - B. Serum Fe concentration.
  - C. Hematocrit concentration.
  - D. Serum ferritin concentration.
21. Which one of the following nutritional deficiencies is present in E.T.?
  - A. Folate.
  - B. Iron.
  - C. Copper.
  - D. Selenium.

**Questions 22–25 pertain to the following case.**

A 42-year-old woman is admitted to the medical ICU after suffering an upper gastrointestinal tract hemorrhage secondary to presumed excessive nonsteroid anti-inflammatory drug intake. The patient is an avid runner and has been training for the Chicago marathon. Her drugs on admission include ibuprofen 800 mg every 4 hours for the past month. She has no other medical history. On admission to the ICU her hemoglobin concentration was 10.5 g/dL, and she was in no hemodynamic compromise. Her only complaint was vomiting of bright red blood yesterday morning. Vital signs include blood pressure 110/72 mm Hg, heart rate 65 beats/minute, respiratory rate 14 breaths/minute, and temperature 37.3°C. Her drugs in the ICU currently include intravenous famotidine, acetaminophen as needed, and intravenous fluids of sodium chloride at 100 mL/hour.

22. The medical ICU director wants to initiate epoetin alfa for this patient. Which one of the following adverse effects would be most likely to occur with the short-term use of epoetin alfa (e.g., for anemia of critical illness) in this patient?
  - A. Hypertension.
  - B. Hypervolemia.
  - C. Edema.
  - D. Deep vein thrombosis.
23. The physician also wants to administer 2 units of packed RBCs to increase the patient's hemoglobin above 12 g/dL. Which one of the following would be the best course of action to manage this patient's anemia at the present time?
  - A. Change her famotidine to sucralfate.
  - B. Monitor hemoglobin concentrations more frequently.
  - C. Recommend against a blood transfusion in this patient.
  - D. Avoid bedside point of care testing in this patient.

After two nights in the ICU, the patient suddenly is complaining of nausea and begins vomiting blood. The patient has also had copious amounts of bright red blood in her stool. Her vital signs are heart rate 110 beats/minute, respiratory rate 18 breaths/minute, temperature 99.0°F degrees, and blood pressure



90/40 mm Hg. Hemoglobin is 8.3 g/dL, prothrombin time is 17.1 seconds, and activated partial thromboplastin time is 47.3 seconds.

24. Which one of the following would be the best reason for administering a packed RBC transfusion in this patient?
- A. Hemoglobin concentration less than 10 g/dL.
  - B. Current hemodynamic compromise.
  - C. A low risk of transfusion.
  - D. To achieve hemostasis.
25. Which one of the following is the most appropriate means of treating coagulopathy in this patient?
- A. Fresh frozen plasma.
  - B. Tranexamic acid.
  - C. Aprotinin.
  - D. Recombinant activated factor VII.