

ANEMIA, BLEEDING, AND BLOOD TRANSFUSION IN THE INTENSIVE CARE UNIT: CAUSES, RISKS, COSTS, AND NEW STRATEGIES

By Michael T. McEvoy, RN, PhD, CCRN, NRP, and Aryeh Shander, MD

CNE 1.0 Hour

Notice to CNE enrollees:

A closed-book, multiple-choice examination following this article tests your understanding of the following objectives:

1. Describe the physiological effects, treatments, and potential outcomes associated with anemia in intensive care unit (ICU) patients.
2. Identify the increased mortality and morbidity associated with anemia in ICU patients and the patients most at risk for these adverse outcomes.
3. Discuss strategies and tools for prevention of anemia, early recognition of bleeding, and avoidance of unnecessary blood transfusions in ICU patients.

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The definition of anemia is controversial and varies with the sex, age, and ethnicity of the patient. Anemia afflicts half of hospitalized patients and most elderly hospitalized patients. Acute anemia in the operating room or intensive care unit is associated with increased morbidity as well as other adverse outcomes, including death. The risks of anemia are compounded by the added risks associated with transfusion of red blood cells, the most common treatment for severe anemia. The causes of anemia in hospitalized patients include iron deficiency, suppression of erythropoietin and iron transport, trauma, phlebotomy, coagulopathies, adverse effects of and reactions to medications, and stress-induced gastrointestinal bleeding. The types and causes of anemia and the increased health care utilization and costs associated with anemia and undetected internal bleeding are described. The potential benefits and risks associated with transfusion of red blood cells also are explored. Last, the strategies and new tools to help prevent anemia, allow earlier detection of internal bleeding, and avoid unnecessary blood transfusions are discussed. (*American Journal of Critical Care*. 2013;22:eS1-eS14)

Anemia, defined by the World Health Organization as a hemoglobin level less than 13 g/dL in men and less than 12 g/dL in women,¹ is an epidemic afflicting one-quarter of the world's population, approximately 50% of hospitalized patients, and up to 75% of elderly hospitalized patients.² A high percentage of patients become anemic during a stay in an intensive care unit (ICU), from 60% to 66% at admission,^{3,4} up to 90% by day 3,⁵ and 97% by day 8.⁶ Data collected during the year 2000 on more than 81 000 health plan members indicate that the highest rates of anemia are in patients with chronic kidney disease (34.5%), cancer (21%), chronic heart disease (18%), inflammatory bowel disease (13%), rheumatoid arthritis (10%), and infection with human immunodeficiency virus (10%).⁷

Causes of Anemia

Anemia may be due to a single factor such as a nutritional deficiency or its cause may be multifactorial. Anemia results from 1 or more of the following events: loss of red blood cells (RBCs), reduction in the production of RBCs, increased destruction of

RBCs, and shorter life span of RBCs. Multiple factors may contribute to the development of complex anemia in hospitalized patients, including nutritional deficiencies, suppression of RBC production by medications, inflammatory cytokines (inflammatory anemia or anemia of chronic disease), phlebotomy and chronic or acute bleeding (Table 1).

Table 1
Anemia in intensive care patients

Type	Causes
Nutritional deficiencies	Low iron levels Low folate levels Low vitamin B levels
Erythropoietin deficiencies	Anemia of chronic disease Renal insufficiency Infection Endocrine disorders
Hemolysis	Drug reactions Toxins
Coagulation abnormalities	Thrombocytopenia Sepsis syndrome Liver disease Viral infection Splénomegaly
Blood loss	Phlebotomy Trauma Surgery Gastrointestinal bleeding

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Nutritional Deficiency Anemia

Although iron deficiency may affect up to 40% of critically ill patients,⁸ the prevalence of ICU patients suffering from nutritional iron deficiency alone is not as high. In 1 study,⁹ researchers reported that 9% of ICU patients were iron deficient, 2% were vitamin B₁₂ deficient, and 2% were deficient in folic acid leading to anemia. However, in a study in older adults, researchers reported that one-third of persons 65 years old and older had nutritional deficiency anemia,¹⁰ so the occurrence of that type of anemia in hospitalized, critically ill adults may be higher than previously suspected. In a healthy person, a significant inverse relationship exists between hemoglobin concentration and levels of erythropoietin, a hormone produced by the kidneys in response to decreased tissue oxygen tension that stimulates the erythroid progenitor cells in the bone marrow to produce RBCs. When oxygen tension in the tissue is low because of low hemoglobin concentration, erythropoietin levels increase to stimulate increased RBC production (erythropoiesis). However, if the body is depleted of iron stores because of nutritional deficiency, hemoglobin synthesis is defective, resulting in the production of smaller and fewer RBCs that contain a reduced amount of hemoglobin. Patients with absolute iron deficiency (serum ferritin <30 µg/L and/or transferrin saturation <20%), leading to iron-restricted erythropoiesis, can be treated with oral iron or with intravenous iron if oral iron is not tolerated. Up to 59% of patients have gastrointestinal

adverse effects from oral iron therapy, so intravenous iron therapy has become the preferred method of repletion in these patients.¹¹

Anemia of Chronic Disease

Approximately 35% of patients who are anemic on admission to the ICU have anemia due to iron sequestration.^{12,13} Iron sequestration, characterized by the inability to release and use iron stores,¹⁴ which leads to iron-restricted erythropoiesis, occurs with inflammatory anemia or anemia of chronic disease. The feedback loop of oxygen tension, erythropoietin levels, and erythropoiesis described previously is disrupted in patients with inflammatory anemia.¹⁵ Similar to patients with chronic inflammatory disease, those with inflammatory anemia have blunted erythropoietin production and down-regulation of erythropoietin receptors in the bone marrow, although many patients retain their responsiveness to erythropoietin.¹⁶ Additionally, release of inflammatory cytokines leads to reduced renal erythropoietin production (thus decreased RBC production) and activation of RBC destruction by macrophages (eryptosis), which not only decreases the absolute number of RBCs but also reduces RBC life span, and decreased responsiveness of the bone marrow to erythropoietin (and thus decreased RBC production). The level of hepcidin, a peptide made up of 25 amino acids produced by the liver, which functions as the master regulator of iron metabolism,⁸ is elevated during inflammatory states, such as occurs with rheumatologic diseases, inflammatory bowel disease, infections, and critical illness.¹⁷ The elevated level of hepcidin is responsible for reduced iron absorption by the gut and increased iron sequestration by macrophages, leading to iron sequestration anemia. For this reason, hepcidin agonists, which prevent iron overload and improve erythropoiesis, and antagonists, to relieve hepcidin-mediated iron sequestration and release more iron for erythropoiesis, are being sought to manage iron sequestration anemia.¹⁸

Iron deficiency may coexist with inflammation, however, and in patients with both those problems, hepcidin levels may be low or variable¹⁷ and intravenous iron therapy alone or in combination with erythropoietin-stimulating agents (ESAs) may be helpful. This area remains controversial. A meta-analysis¹⁹ evaluating the effect of erythropoietin-receptor agonists on transfusion frequency showed a small reduction in RBC transfusions, and with other studies suggesting that erythropoietin therapy is associated with increased rates of clinically rele-

vant thrombotic vascular events, use of ESAs has been dramatically reduced.¹⁶ Conversely, a series of 3 randomized controlled trials (referred to as erythropoietin-1,²⁰ erythropoietin-2,¹⁶ and erythropoietin-3²¹) conducted by Corwin and colleagues showed increased hemoglobin concentration in critically ill patients receiving erythropoietin. The first study²⁰ was a small placebo-controlled trial (n = 160) that showed a nearly 50% reduction in RBC transfusions and higher hematocrit in the group receiving erythropoietin compared with the placebo group. The second, larger trial¹⁶ (n = 1302) showed a 20% decrease in the number of RBC units transfused in the erythropoietin group with similar clinical outcomes in both groups. The third and largest trial,²¹ conducted in 1460 critically ill patients, showed an increase in hemoglobin concentration, no reduction in RBC transfusions, perhaps because of a reduced threshold for transfusion, and an increase in thromboembolic episodes in the erythropoietin group compared with the control group. Considered together, the clinical evidence for erythropoietin therapy in critically ill patients suggests a decrease in mortality in trauma patients (but this effect does not appear to be related to a reduction in RBC transfusions) and an increase in the frequency of adverse events, particularly in patients with cancer or chronic renal failure. Erythropoietin, therefore, is used with caution in critically ill patients unless chronic conditions (such as renal insufficiency) are present and a thorough workup suggests that erythropoietin may be beneficial.²²

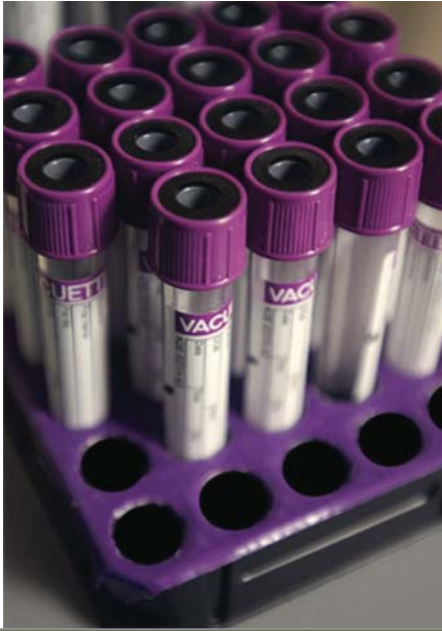
Phlebotomy

Blood loss due to phlebotomy can be another important cause of anemia both in general care areas and in the ICU.³ The normal daily production of RBCs in healthy adults is about 0.25 mL/kg, which translates to approximately half a liter of blood every week. Yet diagnostic phlebotomy can result in a mean daily loss of up to 70 mL of blood per day in an ICU patient,²³ which may be more than can be naturally replaced in a critically ill patient. In a large study²⁴ of 17 676 cardiac patients from 57 hospitals, researchers found that for every 50 mL of blood collected, the risk of moderate to severe hospital-acquired anemia increased 18%. As only a small percentage of the blood collected is

Up to 90% of patients have anemia by day 3 in the intensive care unit.

Anemia in the ICU may be nutritional, a result of chronic disease, or hospital acquired.

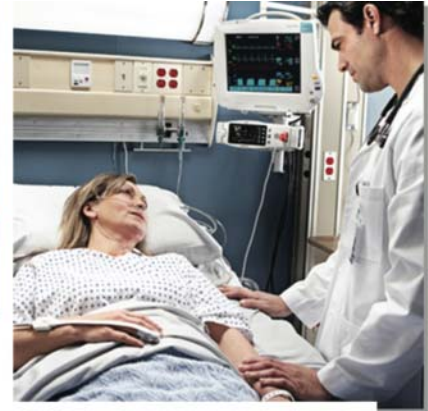
A



B



C



D



Figure 1 Options to reduce blood from phlebotomy: A, pediatric phlebotomy tubes; B, eliminate discarding blood from arterial catheter; C, read through motion and low-perfusion pulse oximetry instead of blood gas analysis; D, multiwavelength pulse co-oximetry for noninvasive and continuous monitoring of hemoglobin level.

Table 2
Drugs commonly linked to hemolytic anemia^a

Mechanism of hemolysis	Common medications
Immune	Cephalosporins/cephamycins Cefotetan Ceftriaxone
	β-lactams Penicillin derivatives Piperacillin
	Nonsteroidal anti-inflammatories Diclofenac Ibuprofen
	Antineoplastics Fludarabine
	Others Methyldopa Quinine/quinidine
Nonimmune	Nitrofurantoin
	Phenazopyridine
	Primaquine
	Sulfa drugs

^a Based on information from Shander et al.²⁶

used for laboratory analysis,²⁵ an opportunity exists for blood conservation strategies to make a significant difference without affecting the collection of physiological data to guide treatment. Strategies to

reduce diagnostic blood sampling include switching to small-volume or pediatric phlebotomy tubes, replacing routine multiple daily phlebotomies for blood sampling only when clinical signs indicate the need, and implementing closed-loop systems that return blood that is ordinarily wasted back to the patient. Point-of-care and inline bedside microanalysis of blood or noninvasive hemoglobin monitoring with pulse co-oximetry are other ways to monitor hemoglobin for anemia while minimizing blood loss (Figure 1).

Drug Reactions

Drugs administered in the ICU may have adverse effects that can lead to anemia by 2 distinct pathways: by causing hemolysis (hemolytic anemia, see Table 2⁶) or by suppressing normal renal release of erythropoietin. Drug-induced hemolytic anemia is a relatively rare but serious adverse effect of therapeutic drugs caused by increased destruction of drug-damaged erythrocytes by macrophages in the spleen and liver. The 3 drugs most often identified as causing drug-induced hemolytic anemia are piperacillin, cefotetan, and ceftriaxone.²⁷ Discontinuation of the drug is the only treatment needed if the antibodies causing the macrophage activation are drug dependent. For drug-independent hemolytic anemia, corticosteroids are a first-line therapy²⁸ followed by rituximab, which reduces levels of macrophages

responsible for hemolysis.²⁹ Drug reactions can also cause anemia in ICU patients by suppression of erythropoietin. Commonly used drugs such as angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers (for treatment of high blood pressure), calcium channel blockers, theophylline, and β -adrenergic blockers suppress release of erythropoietin in some patients.³⁰

Bleeding Complications in the ICU

Bleeding complications in the ICU are common and not restricted to trauma and postsurgical patients. In a study³¹ examining the frequency, severity, and causes of bleeding complications in a medical-surgical ICU, researchers reported that of 100 patients, 90% experienced bleeding, resulting in 480 bleeding events. Twenty percent of patients experienced a major bleeding event lasting a median of 4 days. Only about 15% of bleeding events were at a surgical site, whereas 38% were at the insertion site of the vascular catheter and 16% were at the endotracheal tube site. Although only 6% were gastrointestinal in origin, these events made up more than half of the major bleeding events.

Coagulation abnormalities and stress-induced mucosal lesions are 2 of the most prevalent risk factors for significant bleeding in ICU patients. In coagulopathic patients, retroperitoneal bleeding due to coagulation abnormalities increases mortality³² and results in increased use of resources, including blood components, and extended lengths of stay.³³ Improved detection of occult bleeding may prevent delays in diagnosis and reduce these risks.

Coagulation Abnormalities

Coagulation abnormalities such as thrombocytopenia, consumption of clotting factors, and less commonly, disseminated intravascular coagulation (DIC) are found in critically ill patients. Thrombocytopenia, typically defined as a platelet count of less than 150 000/ μ L, affects up to 45% of patients.³⁴ Thrombocytopenia can be induced by numerous clinical events such as hemodilution from transfusion due to massive blood loss; platelet consumption from trauma, bleeding, or DIC; platelet destruction by immune response such as sepsis syndrome; decreased platelet production caused by liver disease; defective bone marrow or viral infection; and increased splenic sequestration due to splenomegaly.³⁴⁻³⁶ Medications, including some commonly used in the ICU and mechanical cardiac assist devices, have also been implicated in inducing thrombocytopenia.

DIC is far less common, occurring in an estimated 1% of hospitalized patients,³⁷ but it may occur in

up to 50% of patients with severe sepsis.³⁸ It is characterized by an abnormally low platelet count caused by increased consumption of platelets and other coagulation factors and by prolonged coagulation times. Aberrations in endothelial function and altered levels of endogenous procoagulant, anticoagulant, and fibrinolytic factors can all contribute to the development of DIC. Although rare, DIC is an independent predictor of mortality, with the increase in severity directly related to an increase in mortality. Bleeding is perhaps the most obvious clinical sign of DIC, but end-organ damage induced by microvascular thrombosis is responsible for most of the morbidity and mortality.³⁹ Like thrombocytopenia, DIC is thought to be a common feature of both sepsis and trauma, especially neurotrauma, and is often linked to systemic inflammation or infection. DIC can be diagnosed by using a scoring system based on a series of coagulation tests^{40,41} or a ratio of results of specific tests.⁴²

Perhaps because of the complexity of DIC, successful treatment has been elusive,⁴³ but some strides have been made in the prevention of development of DIC by avoiding hemodilution (permissive hypotension), preventing hypothermia and acidosis (which can compromise thrombin-generation kinetics and fibrinogen metabolism),⁴⁴ and revising blood component therapy so that RBCs, fresh frozen plasma, and platelets are transfused in a 1:1:1 ratio, a therapy that is controversial and is still being evaluated.^{32,38,45}

“Stress-Induced” Gastrointestinal Bleeding

In the ICU, occult or visible bleeding may develop as a result of physiological stress caused by clinical interventions or as a result of the stress and the intervention itself. Mechanical ventilation for more than 48 hours and coagulopathy are the 2 major risk factors for stress-induced bleeding in the upper part of the gastrointestinal tract, with respiratory failure being present in almost all affected patients.³³ Other risk factors include traumatic and nontraumatic brain injury, renal failure, liver disease, and gastric ulcers. Although clinically significant and potentially fatal if detected too late, gastrointestinal bleeding is infrequent in ICU patients because of the routine use of histamine-2 receptor antagonists or proton pump inhibitors as prophylaxis. However, it should be noted that mortality rates can be 4 times higher and ICU length of stay can be 4

Blood loss due to phlebotomy, drug reactions, and bleeding complications can cause anemia in ICU patients.

Table 3
Anemia and blood transfusion in the intensive care unit (ICU)

Feature	Anemia	Blood transfusion
Frequency	>60% of ICU patients upon admission ⁴ 90% of ICU patients by day 3 in ICU ⁵ 97% of ICU patients by day 8 ⁶	20% to 62% of ICU patients receive 1 or more units of blood ^{4,55,56}
Increased morbidity and mortality	Associated with increased 90-day mortality in patients with chronic obstructive pulmonary disease ⁵⁷ Associated with adverse outcomes in patients with congestive heart failure, acute myocardial infarction, and chronic kidney disease ⁵⁸⁻⁶⁰	Associated with as much as a 40% increase in 30-day morbidity ⁶¹ Associated with as much as a 38% increase in 30-day mortality ^{56,61}
Increased costs	Associated with >twice inpatient costs in patients with chronic conditions ⁷ Associated with increased length of stay in patients with heart failure ⁶²	Activity costs are \$522 to \$1183 per unit of blood ⁶³ Associated with ≥2 day increase in length of stay per transfusion ⁶⁴

to 8 days longer in those patients in whom significant bleeding develops.^{46,47}

As described earlier, stress ulcer prophylaxis with agents such as H₂-receptor antagonists and proton pump inhibitors have been effective in reducing the number of ICU patients in whom stress-related gastric mucosal bleeding develops, and these therapeutics are generally well tolerated by patients but may be overused. One may question the widespread use of these therapies in the ICU and general care areas, considering the low prevalence of clinically significant bleeding due to stress-induced mucosal lesions in these patients. It has been estimated that the number needed to treat to prevent 1 case of bleeding in the upper part of the gastrointestinal tract is 900 patients.³³ One-third of patients are given some type of stress ulcer prophylaxis upon admission,⁴⁸ and in more than half of these patients, the treatment is continued after discharge.⁴⁹ Yet prolonged use of pharmacologic prophylaxis of stress ulcers has been associated with significant adverse effects such as hip fractures, cardiac events, iron deficiency, *Clostridium difficile* infection, and pneumonia.⁵⁰ So although stress ulcer prophylaxis was started to reduce morbidity and mortality and decrease health care costs due to internal bleeding, overuse of these therapies has actually increased costs and degraded patient care for some. The costs associated with overprescription, an absence of benefit for low-risk patients, and the concomitant risks of prolonged use suggest that stress ulcer prophylaxis should be limited to those patients at known high risk for internal gastrointestinal bleeding.^{51,52}

Experts strongly agree that early enteral feeding is effective in preventing stress ulcers and that antacids should not be used as a preventative measure.^{53,54} Health care strategies with few or no adverse effects that are focused on early detection of bleeding should also be considered as an adjunct to early

enteral feeding. One such strategy is the use of continuous and noninvasive hemoglobin monitoring by pulse co-oximetry, which not only can be used to help clinicians detect a change in hemoglobin level in newly admitted patients but perhaps more importantly can be used for the continuous evaluation of hemoglobin level to detect changes as they occur without requiring collection of a blood sample. Because pulse co-oximetry is noninvasive and uses the same sensor that provides the standard-of-care measurements of oxygen saturation, monitoring does not require an additional sensor.

Costs Associated With Anemia and Bleeding

Both anemia and bleeding are associated with significantly higher health care resource use and costs than those for patients without these conditions (Table 3). Results of a study conducted in 2000, which included records from nearly 2.3 million members of a health care plan, indicated that health care costs for inpatients with chronic conditions such as chronic kidney disease, solid malignant tumors, and congestive heart failure were more than twice as high for patients with anemia as for nonanemic patients with the same conditions and severity.⁷ In another study,⁶² researchers found that patients with heart failure and anemia had longer hospital lengths of stay (8.9 days) than nonanemic patients with heart failure (5.7 days) and had significantly higher mean total hospital charges. Likewise, patients with cancer and anemia had significantly higher total hospital expenditures than did nonanemic patients with cancer. In 2005, Lyman and colleagues⁶⁵ reported that the 6-month mean and standard deviation for inpatient health care cost was \$30 639 (SD, \$74 422) for a patient with cancer and anemia and \$13 152 (SD, \$46 332) for a nonanemic patient with cancer.

The controversy remains whether anemia is an independent risk factor for increased costs and worse outcomes in postoperative patients or just an indicator of disease severity. Results of retrospective studies^{66,67} investigating the role of preoperative anemia on postoperative outcomes have suggested a direct relationship between preoperative anemia and worse outcomes, but in a recent large retrospective study⁶⁸ of more than 145 000 surgeries in anemic patients, researchers concluded that anemia is associated with baseline diseases that increase mortality but is itself a weak independent predictor of increased mortality.

Surgical ICU patients with anemia and postoperative bleeding also incur higher costs and have more complications. Percutaneous coronary intervention is associated with significant risk of postsurgical bleeding, with 13% of patients experiencing minor bleeding and more than 5% requiring transfusion. Bleeding after percutaneous coronary intervention is associated with mortality and increased complications, including thrombocytopenia, anemia, and hematoma, all of which affect hospital length of stay and health care costs.⁶⁹ In a study⁷⁰ published in 2003, researchers reported that the cost of hospitalization due to bleeding complications after percutaneous coronary intervention may exceed \$10 000, owing to increased length of stay and the use of additional resources. A retrospective analysis⁷¹ indicated that anemia was an independent predictor of mortality after percutaneous coronary intervention and was associated with more major adverse cardiac events after 30 days and longer stays. Anemia and transfusions after percutaneous coronary intervention increase morbidity and mortality and contribute to additional treatment costs beyond those directly related to the bleeding complication,⁷⁰ whereas improvement of anemia postoperatively is associated with better long-term clinical outcomes.⁷²

Patients with anemia and/or bleeding in both the medical and surgical ICU have increased morbidity and mortality rates,^{73,74} use more health care resources, and have higher hospital costs than do nonanemic⁷ or nonbleeding patients.⁷⁰ Increased costs are most often due to longer stays and costs associated with blood transfusion and the attendant complications.^{62,75}

Risks and Benefits of Blood Transfusions

RBC transfusion is the most common and fastest means of increasing hemoglobin level, with more than one-third of all ICU patients receiving 1 or more units of RBCs.^{4,55} This number increases to more than 60% of patients whose ICU stay is a week or longer.^{55,76} However, RBC transfusion therapy is also costly (\$522 to \$1183 per unit of blood⁶³) and

associated with many risks including as much as a 40% increase in 30-day morbidity,⁵⁶ as much as a 38% increase in 30-day mortality, and as much as a 67% increase in 6-month mortality.

Marik and colleagues⁷⁷ undertook a systematic review of 45 cohort studies to determine the association between RBC transfusion and unfavorable outcomes in critically ill patients. Outcome measures were mortality, infections, multiorgan dysfunction syndrome, and acute respiratory distress syndrome. In 42 of the 45 studies reviewed, the risks of transfusion outweighed the benefits of treating anemia with transfusion. RBC transfusions were an independent predictor of mortality in 17 of the 18 studies that included death as an outcome and were an independent risk factor for nosocomial infection in all 22 studies that included infection as an outcome. Additionally, the meta-analysis showed that RBC transfusions increased the risk of multiorgan dysfunction syndrome and acute respiratory distress syndrome developing.

Transfusion-related acute lung injury (TRALI), transfusion-associated circulatory overload (TACO), and transfusion-related immunomodulation (TRIM), leading to nosocomial infections and increased cancer recurrence, are some of the most common adverse events associated with transfusion of blood components. Additionally, repeated transfusions of RBCs for treatment of chronic conditions can lead to iron overload and result in end-organ damage. The risks of transfusion of blood components therefore must be weighed against the risks of anemia and the risks of other treatments for anemia such as administration of ESA or iron.

TRALI

TRALI is the most easily identifiable cause of transfusion-related morbidity and mortality in the United States.⁷⁸ However, because of the varied criteria used to diagnose this syndrome, the true incidence is not known. In a 2012 study,⁷⁹ researchers reported the rate of TRALI occurrence to be 8.1 (95% CI, 4.4-14.9) cases per 100 000 units of blood components transfused. Risk factors for TRALI are age, illness severity, and (in cardiac surgery patients) time on cardiopulmonary bypass.⁸⁰ As with many other adverse events related to RBC transfusion, the risk for development of TRALI increases with the number of units transfused (Figure 2).⁸¹

Increased costs for patients with anemia and/or bleeding are mostly due to longer stays and costs of transfusion and its complications.

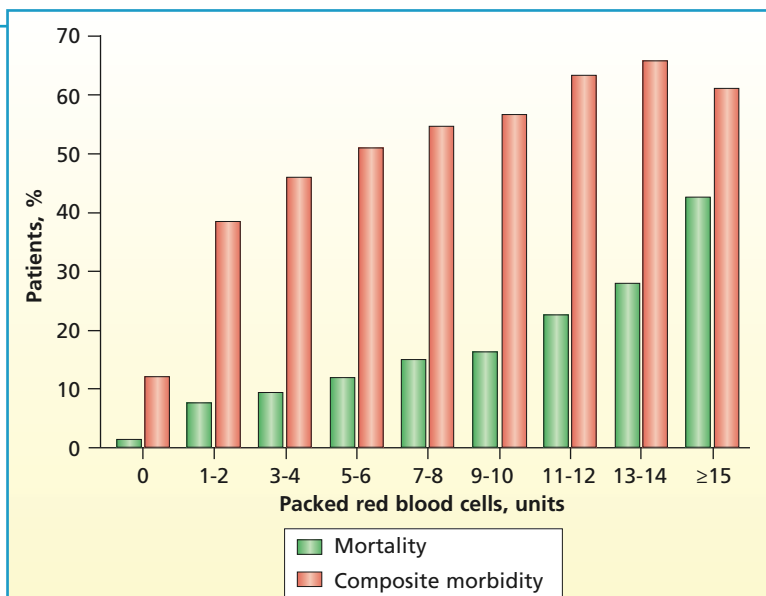


Figure 2 Unadjusted mortality and composite morbidity rates by number of units of packed red blood cells received in intra-operative blood transfusion.

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TRALI is characterized by pulmonary edema, hypoxemia, respiratory distress, and radiographic evidence of new bilateral pulmonary infiltrates (sometimes described as white lung) occurring within minutes to 6 hours after transfusion.⁸² Signs and symptoms may also include fever, tachycardia, cyanosis, hypotension, and frothy sputum.⁸³ TRALI can be triggered by the transfusion of any blood product but the risk is increased with transfusion of blood products with high plasma content⁸⁴ and blood products containing human leukocyte antibodies I and II and human neutrophil antibodies.

The pathogenesis of TRALI is still being elucidated but is thought to be a “2-hit” process,⁸⁵ with the first hit being the presence of an inflammatory condition in the patient that primes monocytes.^{85,86} In the presence of matched class II human leukocyte antibodies in the transfused blood product (the second hit), monocytes become activated and in turn activate neutrophils to release oxidases and other reactive substances that attack the capillary membrane.^{82,87} The leukocyte antibodies are mostly detected in blood components donated from previously pregnant women, so screening of women donors for leukocyte antibodies has reduced the incidence of TRALI.⁸⁸ In a prospective study⁷⁹ in cardiac surgery patients, researchers found that patients in whom TRALI developed spent more time undergoing mechanical ventilation and had longer ICU stays and higher mortality rates than did patients who received transfusions but did not have TRALI develop, so although it is somewhat rare, TRALI is

a serious condition that affects both patients’ outcomes and health care costs.

TACO

TACO occurs when a patient is unable to compensate for rapid or high-volume infusions of blood products. Patients predisposed to volume overload, such as those with congestive heart failure, renal failure, and respiratory failure who require large or multiple transfusions are most at risk for TACO developing. After TRALI, TACO was the most common cause of transfusion-related mortality reported to the Food and Drug Administration in 2010.⁸⁹

Although the incidence of TRALI is declining because of the restriction of female plasma donors, the incidence of TACO appears to be increasing, probably because of increased reporting. In 1 study,⁸⁹ the prevalence of TACO is estimated to be 1 in 68 (95% CI, 1 in 250 to 1 in 27) patients receiving plasma. These patients, on average, received multiple units of plasma (mean, 4.0 units; SD, 2.3 units) before TACO developed.⁸⁹ In a 2-year prospective cohort study⁹⁰ of 901 ICU patients, researchers reported that TACO developed in 6% of patients who received a transfusion. Significant risk factors were left ventricular dysfunction and transfusion of fresh frozen plasma to treat overuse of anticoagulants.⁹⁰ Signs and symptoms of TACO may include lung crackles and rales, elevated jugular venous pressure, dyspnea, orthopnea, wheezing, tightness in the chest, cough, cyanosis, tachypnea, a rapid increase in blood pressure, and distended neck veins. Because TACO has many of the same signs and symptoms as TRALI, the 2 conditions can be difficult to distinguish and in fact may coexist in a patient. Like TRALI, TACO is associated with prolonged ICU and hospital stays and greater intensity of care—although only TRALI is associated with decreased long-term survival.⁹¹

TRIM

The risk of disease transmission through blood transfusions has decreased significantly since the mid-1980s⁹² because of the adoption of pathogen-reduction technologies and sophisticated hemovigilance systems. But, although noninfectious adverse events such as TRALI, TACO, and hemolytic transfusion reactions cause most of the morbidity and mortality associated with blood transfusions in the United States today, TRIM, which can lead to the onset of nosocomial infection, remains a significant problem.

It is not entirely clear how blood transfusion suppresses immune function, but it is likely that multiple factors conspire to initiate a cascade of

events that results in the down-regulation of the recipient's immune system. Because the storage time of red blood cells is associated with bacterial infections in critically ill trauma patients,⁹³ soluble mediators that concentrate in stored RBCs have been implicated in the initiation of the immune suppression cascade. The role of leukocytes in the cascade is not clear because studies of leukoreduction and removal of white cell soluble factors of transfused blood have shown conflicting results.^{93,94} Candidate molecules that may be important in the activation of TRIM continue to be investigated. How the biochemical, structural, inflammatory, and physiological properties of RBCs change with storage, and if any of these changes affect clinical outcomes in patients who receive transfusions, also requires further investigation.⁹⁵

Strategies to Prevent Unnecessary Blood Transfusion

Multiple randomized controlled trials^{64,96} and a recent meta-analysis of 19 trials involving 3746 patients⁹⁶ support the use of restrictive transfusion strategies (transfusing at a lower hemoglobin level). A consensus conference publication⁹⁷ that included a review of 494 studies and 450 clinical scenarios showed that 88% of allogeneic blood transfusions were inappropriate (defined as resulting in either a worse clinical outcome or demonstrating no benefit) and only 12% were clearly appropriate. These trials have raised the awareness of the poor benefit to risk ratio associated with allogeneic blood transfusions in all patients and the need to initiate practice changes.

Clinicians, hospitals, and health care and regulatory agencies are beginning to develop and implement strategies to prevent unnecessary transfusions. The call to reduce blood transfusion is supported by The Joint Commission, which recently introduced patient blood management measures for hospitals to evaluate the appropriateness of transfusions as a continuous quality indicator.⁹⁸ Additionally, the American Medical Association, The Joint Commission, and the Centers for Medicare and Medicaid Services joined to identify RBC transfusions as 1 of the top 5 overused procedures in medicine.

The College of American Pathologists,⁹⁹ the American Society of Anesthesiologists,¹⁰⁰ Society of Critical Care Medicine,¹⁰¹ and the American Association of Blood Banks¹⁰² have all published transfusion guidelines that promote restrictive transfusion triggers for most patients. Although many transfusion guidelines start with addressing surgical patients (eg, treating perioperative anemia and coagulopathy and reducing surgical blood loss), some of the proposed strategies are also relevant to critical care, for

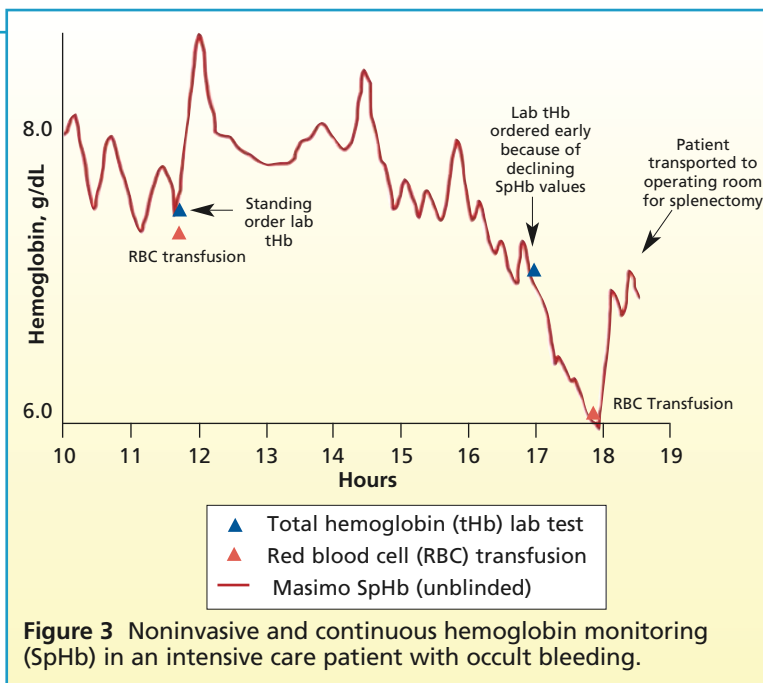
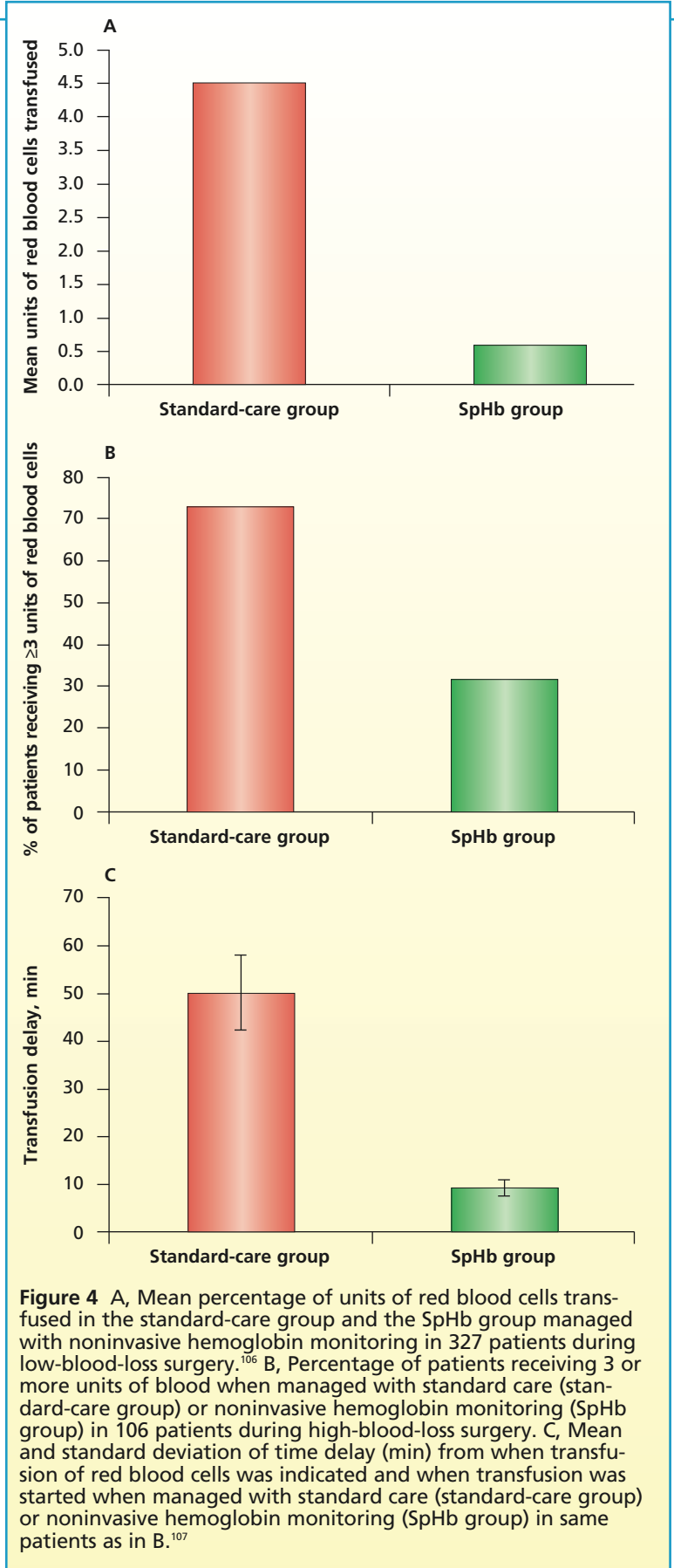


Figure 3 Noninvasive and continuous hemoglobin monitoring (SpHb) in an intensive care patient with occult bleeding.

example, withholding plasma transfusion in the absence of coagulopathy or high risk for bleeding,²² use of single-donor platelets collected from male donors, avoidance of pooled blood products,¹⁰³ minimizing blood loss due to phlebotomy,²⁵ and the close monitoring of postoperative bleeding.

Practice guidelines for RBC transfusion in ICU patients, issued jointly by the Eastern Association for the Surgery of Trauma and the Society of Critical Care Medicine in 2009, recognized the value of transfusion for hemodynamically unstable, acute hemorrhagic shock states and for patients with low oxygen delivery. The guidelines cautioned against use of hemoglobin as a transfusion trigger and recommended against transfusion to facilitate ventilator weaning, recognizing that any transfusion has clear risks and complications. Excepting active acute hemorrhage, RBCs should be transfused 1 unit at a time followed by careful reassessment.⁸⁴

The 2013 Patient Safety Science and Technology Summit¹⁰⁴ released an action plan that included multiple strategies to address overuse of RBC transfusion in both surgical and ICU patients. Proposed strategies include aligning hospital leaders to develop a comprehensive plan to address overtransfusion, implementing changes in the process of care, and using technology. Some specific strategies include reducing unnecessary collection of blood samples for laboratory testing, implementing restrictive transfusion practices, documenting hemoglobin levels before the transfusion of each RBC unit, and using noninvasive and continuous hemoglobin monitoring. Noninvasive and continuous hemoglobin monitoring (Figure 3) is a relatively new tool



that may prove effective for both minimizing blood loss due to phlebotomies when the trended hemoglobin level is stable, avoidance of transfusion through ongoing surveillance, and detection of postoperative or occult ICU bleeding. Noninvasive hemoglobin monitoring has clinically acceptable accuracy in the ICU,¹⁰⁵ but its greatest value may be realized as a trend monitor to detect changes in hemoglobin level earlier, allowing more timely treatment or to assure the clinician that hemoglobin levels are stable, perhaps preventing overtransfusion.

Two studies^{106,107} that showed that noninvasive hemoglobin monitoring helped clinicians avoid blood transfusions during surgery may have implications for practice change that are transferable to the ICU. A randomized controlled trial¹⁰⁶ in orthopedic, low-blood-loss surgery patients showed that the frequency of blood transfusions dropped 87% from 4.5% to 0.6% and the mean units transfused decreased 90% from 0.1 to 0.01 units per patient when noninvasive hemoglobin monitoring was added to standard care. Another study¹⁰⁷ conducted in neurosurgery patients at risk for high blood loss showed that the addition of noninvasive hemoglobin monitoring to standard care resulted in a 47% reduction in the mean number of RBC units transfused (from 1.9 [SD, 2.3] units to 1.0 [SD, 1.5] units) and a 56% reduction in the frequency of multiunit RBC transfusions (73% vs 32%). Additionally, clinicians were able to initiate transfusions 82% faster (in about 9 minutes, compared with about 50 minutes for patients not having total hemoglobin level monitored, $P < .001$) because they did not have to wait for a laboratory hemoglobin value (Figure 4).

Continued research on the clinical utility of this emerging technology in the intensive care setting may identify additional ways this new tool can be useful in blood management.

Conclusion

Anemia and internal bleeding are significant patient care issues associated with increased use of clinical resources, poorer outcomes, and increased costs for patients. Anemia in the ICU may be nutritional, a result of chronic disease, or hospital acquired (anemia due to phlebotomy, coagulopathies, drug reactions, and stress-induced gastrointestinal bleeding). Each type of anemia has a different physiological etiology and requires individualized treatment. Blood transfusion, the most common treatment for severe anemia of any kind, has been linked to significant morbidity and mortality in critically ill patients (Figure 5). Although the number of transfusion-acquired infections has decreased in recent

years, development of TRALI, TACO, TRIM, transfusion reactions, and iron overload in patients receiving multiple transfusions remains a concern.

Practice changes to avoid anemia and blood transfusions include using intravenous iron therapy, reducing diagnostic blood sampling, using small-volume phlebotomy tubes, minimizing or replacing routine phlebotomy, and using point-of-care or inline microanalysis of blood or noninvasive hemoglobin monitoring to measure hemoglobin levels. Earlier detection of bleeding in ICU patients may be achieved by endoscopic evaluations as soon as signs or symptoms are noticed and use of continuous noninvasive hemoglobin monitoring to detect sudden changes in hemoglobin level as they occur. Strategies to prevent unnecessary transfusions in the ICU include restrictive transfusion practices, documenting hemoglobin level before each unit of blood is transfused, and using noninvasive and continuous hemoglobin monitoring. Patient blood management in the ICU is a complex issue that requires balancing the risks of the disease states and adverse effects of the treatments against the benefits of the treatments. Wide-scale changes in clinical practice are needed to implement health care strategies that address both sides of this equation.

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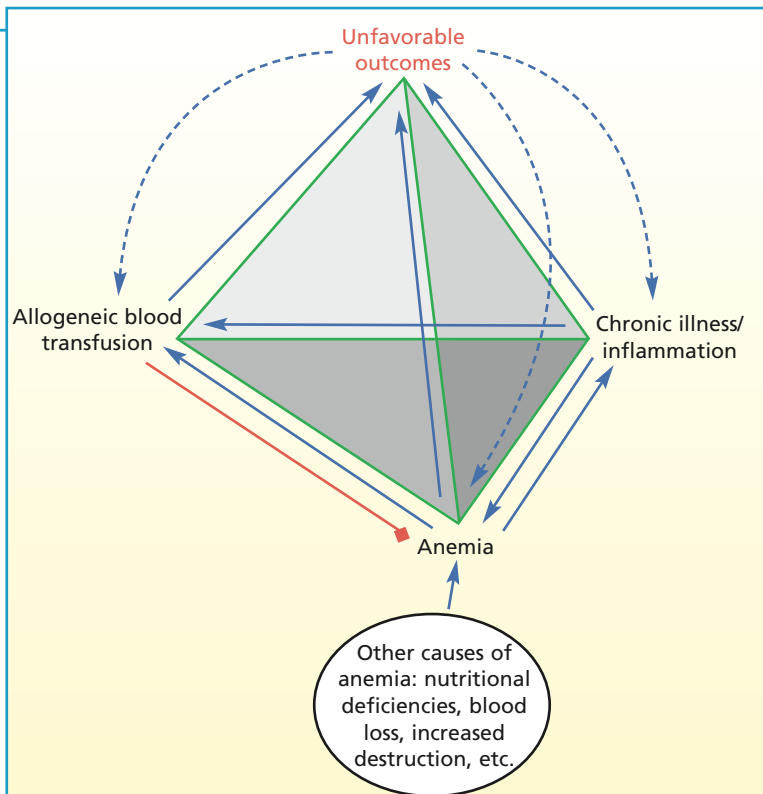


Figure 5 Causal pyramid depicting the theoretical relationship of anemia, illness, and blood transfusion causing unfavorable outcomes. Positive causal links are denoted by solid arrows. Negative causal links are denoted by dashed arrows. Unfavorable outcomes can include occurrence of new morbid events or exacerbation of pre-existing ones, which could lead to increased chronic illness/inflammation burden and further reinforce the loop.

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CNE Test Test ID A132264: Anemia, Bleeding, and Blood Transfusion in the Intensive Care Unit: Causes, Risks, Costs, and New Strategies

Learning objectives: 1. Describe the physiological effects, treatments, and potential outcomes associated with anemia in intensive care unit (ICU) patients. 2. Identify the increased mortality and morbidity associated with anemia in ICU patients and the patients most at risk for these adverse outcomes. 3. Discuss strategies and tools for prevention of anemia, early recognition of bleeding, and avoidance of unnecessary blood transfusions in ICU patients.

1. Which of the following occurs as a result of defective hemoglobin synthesis?

- a. Aberrations in endothelial function
- b. Methemoglobinemia
- c. Absolute iron deficiency
- d. Production of fewer and smaller red blood cells

2. Which of these therapies might be used for treatment of a patient with both inflammatory anemia and iron deficiency anemia?

- a. Erythropoietin stimulating agents
- b. Corticosteroids
- c. Anti-inflammatory agents
- d. Immunosuppressants

3. A patient with which of the following conditions would likely have the highest risk for reduced iron absorption by the gut?

- a. Infection with human immunodeficiency virus
- b. Folic acid deficiency
- c. Rheumatologic disease
- d. Reduced hepcidin levels

4. Which of the following is most closely associated with iron-restricted erythropoiesis?

- a. Anemia of chronic disease
- b. Hemolytic anemia
- c. Coagulation abnormalities
- d. Disseminated intravascular coagulation (DIC)

5. Noninvasive and continuous hemoglobin monitoring would be most beneficial in determining the need for transfusion of red blood cells (RBCs) in which of the following patients?

- a. One with active, acute hemorrhage
- b. One whose trended hemoglobin level is stable
- c. A female with a hemoglobin level of 10 g/dL
- d. A male with a hemoglobin level of 10 g/dL

6. Stimulation of increased RBC production occurs as a direct result of low levels of which of the following?

- a. Serum ferritin
- b. Transferrin saturation
- c. Oxygen saturation
- d. Tissue oxygen tension

7. Administration of which of the following medications would most likely lead to antibody-related activation of macrophages in the spleen and liver, with resultant increased destruction of erythrocytes?

- a. Theophylline
- b. Cephalexin
- c. Cefotetan
- d. Retuximab

8. Release of inflammatory cytokines leads to which of the following effects?

- a. Decreased renal sensitivity to hepcidin
- b. Down regulation of erythropoietin receptors in bone marrow
- c. Stress-induced thrombocytopenia
- d. Increased splenic sequestration due to splenomegaly

9. ICU patients on mechanical cardiac assist devices are most at risk for developing which of the following coagulation abnormalities?

- a. DIC
- b. Consumption of clotting factors
- c. Thrombocytopenia
- d. Hemolysis

10. "Stress-induced" gastrointestinal bleeding is most likely to occur in a patient with which of the following?

- a. Preexisting gastric ulcers
- b. Mechanical ventilation for 48 hours or more
- c. Chronic renal failure
- d. Traumatic or nontraumatic brain injury

11. Which of the following is of most concern as an adverse effect of repeated transfusions of RBCs for treatment of chronic conditions?

- a. Hip fracture
- b. Hemodilution-related coagulopathies
- c. Iron overload
- d. DIC

12. Radiographic evidence of new bilateral pulmonary infiltrates following transfusion of blood components is most likely indicative of which of these common adverse events?

- a. Cancer and/or tumor recurrence
- b. Transfusion-related acute lung injury
- c. Transfusion-associated circulatory overload
- d. *Clostridium difficile* pneumonia

Test ID: A132264 Contact hours: 1.0; pharma 0.0 Form expires: November 1, 2016. Test Answers: Mark only one box for your answer to each question.

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Fee: AACN members, \$0; nonmembers, \$10 Passing score: 9 correct (75%) Category: CERP A Test writer: Ann Lystrup, RN, BSN, CEN, CFRN, CCRN, CSPI

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Program evaluation

- | | Yes | No |
|--|--------------------------|--------------------------|
| Objective 1 was met | <input type="checkbox"/> | <input type="checkbox"/> |
| Objective 2 was met | <input type="checkbox"/> | <input type="checkbox"/> |
| Objective 3 was met | <input type="checkbox"/> | <input type="checkbox"/> |
| Content was relevant to my nursing practice | <input type="checkbox"/> | <input type="checkbox"/> |
| My expectations were met | <input type="checkbox"/> | <input type="checkbox"/> |
| This method of CE is effective for this content | <input type="checkbox"/> | <input type="checkbox"/> |
| The level of difficulty of this test was: | | |
| <input type="checkbox"/> easy <input type="checkbox"/> medium <input type="checkbox"/> difficult | | |
| To complete this program, it took me _____ hours/minutes. | | |

Name _____

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City _____ State _____ ZIP _____

Country _____ AACN Customer ID# _____

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