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RED BLOOD CELL TRANSFUSION IN THE EMERGENCY DEPARTMENT

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☐ **Abstract—Background: Transfusion of red blood cells (RBCs) is the primary management of anemia, which affects 90% of critically ill patients. Anemia has been associated with a poor prognosis in various settings, including critical illness. Recent literature has shown a hemoglobin transfusion threshold of 7 g/dL to be safe. This review examines several aspects of transfusion. Objective: We sought to provide emergency physicians with an updated review of indications for RBC transfusion in the emergency department. Discussion: The standard hemoglobin transfusion threshold was 10 g/dL. However, the body shows physiologic compensatory adaptations to chronic anemia. Transfusion reactions and infections are rare but can have significant morbidity and mortality. Products stored for <21 days have the lowest risk of reaction and infection. A restrictive threshold of 7 g/dL is recommended in the new American Association of Blood Banks guidelines and multiple meta-analyses and supported in gastrointestinal bleeding, sepsis, critical illness, and trauma. Patients with active ischemia in acute coronary syndrome and neurologic injury require additional study. The physician must consider the patient's hemodynamic status, comorbidities, risks and benefits of transfusion, and clinical setting in determining the need for transfusion. Conclusions: RBC transfusion is not without risks, including transfusion reaction, infection, and potentially increased mortality. The age of transfusion products likely has no effect on products before 21 days of storage. A hemoglobin level of 7 g/dL is safe in the setting of critical illness, sepsis, gastrointestinal bleeding, and trauma. The clinician must evaluate and transfuse based on the clinical setting and patient hemodynamic status rather than using a specific threshold.** © **2016 Elsevier Inc. All rights reserved.**

☐ **Keywords—blood product; indications; product age; RBC; transfusion; transfusion reaction**

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INTRODUCTION

Transfusion of red blood cells (RBCs) has been a standard of care for the management of anemia for >100 years. RBC transfusion is common, with approximately 15 million units transfused annually in the United States (US), with 85 million units transfused worldwide (1,2). It was thought that patients would not tolerate anemia and regular transfusion would improve outcomes with little risk. The definition of anemia includes hemoglobin (Hgb) <12 g/dL in females and 13 g/dL in males (3). In fact, anemia affects almost 90% of patients in the intensive care unit during their admission, with 30% of intensive care unit (ICU) admissions possessing a Hgb <9 g/dL and 70% <12 g/dL at the time of admission (4–6). Approximately 40% of critical patients will receive a transfusion during hospitali-zation, receiving on average 2 to 5 units of RBCs (7,8). Anemia in the setting of older age, critical illness, trauma, and surgery has been associated with poor prognosis, as indicated in several studies (9–16).

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Patients in the setting of critical illness have multiple causes of anemia, including active hemorrhage, blunted erythropoietin production, inflammatory cytokine production, increased hepcidin, iron deficiency, and underlying disease (e.g., renal failure). RBC transfusion in anemia can increase oxygen delivery, increase cell mass, and potentially resolve anemic symptoms; however, transfusion can contribute to fluid overload, fever, reaction, immunomodulation, multiple organ dysfunction, hypothermia, and coagulopathy (17).

The standard level for transfusion was considered to be Hgb of 10 g/dL or hematocrit (Hct) <30% (15,18–20). Therefore, many transfusions occurred in patients with little to no symptoms in an effort to maintain Hgb levels above this number, considered a liberal strategy for transfusion. Several recent studies have questioned the liberal transfusion threshold in patients with sepsis, gastrointestinal (GI) bleeding, acute coronary syndrome (ACS), and trauma, as well as other components of product transfusion, including the physiologic effects of transfusion, product reactions, and effect of RBC product age.

The question for providers caring for patients ultimately revolves around the threshold for transfusion. Within emergency medicine, critical care, and in-hospital settings, little debate currently exists on restrictive strategy for hemodynamically stable admitted patients. Most would also agree that transfusion can be life-saving in patients with hypoperfusion and severe bleeding. This review will discuss the recent literature on these points and provide emergency physicians with an evidence-based review on the indications for RBC transfusion.

DISCUSSION

Physiologic Effects of RBC Transfusion

Oxygenation is dependent on Hgb concentration, Hgb saturation, oxygen supply, cardiac output, and pulmonary extraction and perfusion. Oxygen delivery to tissues occurs predominantly through attachment to Hgb. A large reservoir of oxygen delivery exists, as the rate of delivery in the normal individual exceeds the consumption of oxygen by a factor of 4; however, if Hgb decreases, oxygen delivery may be affected (21,22).

In a healthy adult, the normal daily production of RBCs is 0.25/kg, with an average RBC lifespan of 120 days—transfused blood cells have a lifespan of 60 days (23). One unit of RBCs increases Hgb by 1 g/dL and Hct by 3%, but these levels may not be reached in the setting of occult bleeding, repeated laboratory draws, fever, hypersplenism, immunologic disease, or hemolysis (23–26). RBCs can be stored to a maximum of 42 days. The process of storing RBCs changes cell wall deformability, increases proinflammatory cytokines, and decreases 2,3-diphosphoglycerate (2,3-DPG), which shifts the oxyhemoglobin dissociation curve to the left. In fact, levels of 2,3-DPG are depleted within 2 weeks of storage, decreasing the ability of RBCs to release oxygen to peripheral tissues. Product transfusion can increase intrinsic blood viscosity and decrease cardiac output, and these effects actually diminish the ability of RBCs to improve oxygenation in critically ill patients (4,15–17,22,24,25). Whether product storage age affects patient morbidity and mortality is controversial, which will be discussed later.

Exogenous RBC ability to increase oxygenation of tissues is not well established in the literature. In the setting of anemia, the body shows a number of physiologic compensatory methods by increasing cardiac output and oxygen extraction in the tissues, as well as an increased ability to offload oxygen in the peripheral tissues through increased 2,3-DPG levels in RBCs. Coronary artery blood blow increases, and blood flow can redistribute through intravascular vasodilators to where it is most needed. With these measures, the body can adapt to chronic anemia (21,22,27).

Types of Products

There are several types of RBCs, each with specific indications to reduce the risk of transfusion reaction. The majority of these situations involve patients with comorbidities, usually immunosuppression, or patients who have received multiple transfusions.

Leukoreduced. The indications for leukoreduced or leukodepleted RBCs include prevention of febrile nonhemolytic reaction, caused by the presence of antibodies to white blood cells (WBCs). Other indications include reduction in the risk of cytomegalovirus (CMV) infection (e.g., bone marrow transplant patients, pregnant women, and patients with HIV/AIDS), reduction in the risk of transplant rejection, and intrauterine transfusions. Leukocyte-reduced products contain fewer WBCs ($<5 \times 10^6$ WBCs) through leukocyte reduction filters (28,29).

Washed. Washed RBCs are used to prevent allergic reactions, specifically in patients with immunoglobulin A deficiency, and in patients with recurrent severe transfusion reactions not prevented by pretreatment with antihistamines and corticosteroids. Centrifugation separation removes close to 98% to 99% of the plasma constituents, decreasing antigens in the plasma and RBC membrane. Washed units often do not provide the full 1-g/dL increase in Hgb, because 10% to 20% of the cells are lost (28,29).

Irradiated. Irradiation of products is completed to prevent transfusion-associated graft vs. host disease (TAGVHD) through the gamma irradiation of products. Whole blood cells, RBCs, platelets, and granulocytes can undergo irradiation between 25 to 50 Gys, but this does reduce the shelf life of the product (29–31).

Transfusion Reactions and Infections

Transfusion of RBCs functions as an allogeneic tissue transplantation, which is associated with risk. Patients and medical providers are often most concerned with infection transmission or transfusion reaction. Transfusing RBCs introduces foreign antigens into the patient, and the host response varies with modifications to intrinsic T cells, lymphocyte response, natural killer cell function, cytokine production, and phagocyte function. This effect is known as transfusion-related immunomodulation (TRIM), which may be associated with increased adverse effects of transfusion (32).

Not only does TRIM occur, but each unit transfused has other associated risks, such as infection and transfusion reaction. Regarding the risk of infection, 1 meta-analysis found an absolute pooled risk of serious infection of 11.8% with the restrictive strategy vs. 16.9% with a liberal strategy. The number needed to treat with a restrictive rather than a liberal RBC transfusion policy in order to prevent 1 serious infection was 38 (33). Another study found that each RBC unit transfused increased risk of infection by 29% in post–cardiac surgery patients (34). In a study focusing on critically ill patients, a nosocomial infection rate of 24.3% in patients receiving a transfusion was found, vs. 10.2% in those not transfused (35).

In developed nations with well-regulated supplies, safety of transfusion has drastically improved because of changes in blood screening measures and quality control. The risk of HIV, hepatitis C virus, and hepatitis B virus in Canada is 1 per 7.8 million donations, 1 per 2.3 million donations, and 1 per 153,000 donations, respectively (36). In the US, the risk of HIV transmission is 1 per 1.5 million and hepatitis B virus 1 in 357,000 donations. Unfortunately, the story is different in developing nations, with 39 countries not testing donated units. The prevalence of HIV in low-income nations is 2.3% of the blood donations obtained (37–41).

Other transfusion reactions include febrile nonhemolytic transfusion reaction, allergic reaction, acute hemolytic reaction, anaphylactic reaction, transfusion-associated circulatory overload (TACO), transfusion-associated acute lung injury (TRALI), iron overload, delayed hemolytic reaction, and (TAGVHD) (42–45). These risks are discussed in greater detail in Table 1.

Effect of Product Age

Regulations allow the storage of products $\leq$ 42 days, though the majority of transfusions include products stored 16 to 21 days, and physiologically it would seem RBCs stored for greater lengths of time would be associated with poorer outcomes (5,7). Proposed mechanisms include increased inflammatory activity, increased adhesion of the cell membrane to vasculature, decreased 2,3-DPG, and increased deformation of stored RBCs (45–54). However, debate exists on the effects of product age and morbidity and mortality in critically ill patients.

A 2008 study in the *New England Journal of Medicine* found that products stored for a longer time period (20 days) vs. a shorter period (11 days) were associated with mortality (2.8% vs. 1.7%; $p = 0.004$), intubation beyond 72 hours (9.7% vs. 5.6%; $p < 0.001$), renal failure (2.7% vs. 1.6%; $p = 0.003$), and sepsis or septicemia (4.0% vs. 2.8%; $p = 0.01$). The primary population included patients obtaining some form of cardiac surgery, and the authors claim RBC units stored $\geq$2 weeks have higher risks associated with transfusion (35). A systematic review with 18 observational studies and 409,966 patients found a 16% increase in mortality (55). In fact, 1 study found that patients receiving older RBCs (stored for 14–42 days) had higher rates of sepsis (4.0% vs. 2.8%; $p = 0.01$), intubation > 72 hours (9.7% vs. 5.6%; $p < 0.001$), renal failure (2.7% vs. 1.6%; $p = 0.003$), and in-hospital mortality (2.8% vs. 1.7%; $p = 0.004$) (56).

However, this literature conflicts with other studies noting no effect of product age with patient outcomes—mortality in particular. A 2015 *New England Journal of Medicine* article in a similar group undergoing cardiovascular surgery compared transfusion with products <10 days old vs. >21 days old. Mortality was not statistically significant between the groups (57). One randomized trial did not document adverse consequences on oxygenation, immunologic, or coagulation variables in 50 patients undergoing mechanical ventilation who received RBC units that had been stored for a median of 4.0 days, as compared with 50 patients who received blood that had been stored for 26.5 days (58). Another recent study evaluating the age of products transfused in critically ill patients admitted to an ICU found that products stored for a mean ($\pm$ SD) of 6.1 $\pm$ 4.9 days as compared with 22.0 $\pm$ 8.4 days in the standard blood group ($p < 0.001$) had no clinically significant effect on mortality, major illness, duration of hospital stay, intensive support, or transfusion reaction (59).

A Cochrane review from 2012 stated that insufficient literature existed for full recommendations in patients with ACS, critical illness, trauma, or the perioperative

Table 1. Transfusion Reaction Classification (42–45)

Reaction	Pathophysiology	Symptoms	Occurrence (Units Transfused)
Febrile nonhemolytic reaction	Recipient antibodies react with antigens in the product provided and increased cytokines in product	Fever, often low grade; resolves with acetaminophen	Approximately 1 in 100–500 units transfused
Bacterial infection	Products can provide medium for bacterial growth; risk highest with platelet products	High fever, chills, hypotension, rigor, and nausea/vomiting	1 in 250,000 units transfused
Allergic	Exposure to foreign plasma proteins, often in patients with IgA deficiency	Urticaria, pruritis, hypotension, and nausea/vomiting; may meet criteria for anaphylaxis	1 in 333 units transfused; anaphylactic reaction in 1 in 20,000 units
Acute hemolytic reaction	ABO incompatibility results in immune reaction and destruction of transfused cells	Symptoms of anaphylaxis with hypotension, tachycardia, confusion, dysrhythmia, shock, cardiac arrest, and dyspnea	1 per 250,000–600,000 units transfused
Transfusion-associated acute lung injury	Transfused cytokines and interaction of patient WBC with antibodies in donor	Acute respiratory distress with fever, pulmonary edema, and hypotension; symptoms within 2–8 hours	1 in 5000–150,000 units transfused.
Transfusion-associated circulatory overload	Edema, dyspnea, orthopnea, and hypertension	Volume overload seen in patients with impaired cardiac function	Varies with disease presence and comorbidities; approximately 1–8 in 100 units transfused
Delayed hemolytic reaction	Fever, jaundice, and darkened urine; may have subclinical reaction with minimal symptoms	Patient antibodies to RBC antigens, often in patients with previous transfusion; shortened RBC survival	Unknown
Transfusion-associated graft vs. host disease	Variety of presentations ranging from anaphylaxis to tachycardia, fever, and hypotension; often fatal	Immunologic attack of transfused cells against recipient, most often in immunosuppressed patients	1 in 100–1000 units transfused in patients with malignancy
Iron overload	Liver and endocrine dysfunction, cardiotoxicity with dysrhythmia, and congestive heart failure may also occur	One unit of transfused RBC contains 2 mg of iron; threshold of clinically significant iron overload likely at 10–20 units of RBC transfused	Unknown

IgA = Immunoglobulin A; RBC = red blood cell; WBC = white blood cell.

state. The existing studies suffer from extensive heterogeneity, different definitions of "old" vs. "fresh" products, and significant study bias, and the authors of both reviews call for further randomized study (60). Currently, insufficient evidence exists that true harm is present with older products. Studies are retrospective in design, observational, and have small sample sizes (61). Several randomized trials are currently underway evaluating the effect of transfusion age. However, if possible, products < 21 days should be given, with studies suggesting harm with older products (i.e., those stored for > 21 days).

Transfusion Guidelines

Multiple guidelines for transfusion exist. The most commonly referenced includes the American Association of Blood Banks (AABB). Other guidelines from the American Society of Anesthesiology, British Committee for Standards in Hematology, European Society of Cardiology, Australian and New Zealand Society of Blood Transfusion, and American College of Physicians have similar recommendations (62–65). AABB recommendations include the following (66):

1. Adhere to a restrictive transfusion strategy (7–8 g/dL) in hospitalized, stable patients (grade: strong recommendation; high-quality evidence)
2. Adhere to a restrictive strategy in hospitalized patients with pre-existing cardiovascular disease and considering transfusion for patients with symptoms or a Hgb level of ≤8 g/dL (grade: weak recommendation; moderate-quality evidence)
3. No recommendation for or against a liberal or restrictive transfusion threshold for hospitalized, hemodynamically stable patients with ACS (grade: uncertain recommendation; very low-quality evidence)
4. Transfusion decisions be influenced by symptoms and Hgb concentration (grade: weak recommendation; low-quality evidence)

These clinical guidelines serve an important purpose in management, but these can be misapplied to

populations outside of the intended patients, and the recommendations are often misinterpreted in that a liberal transfusion policy is always harmful.

Instead of following a strict number for transfusion threshold based on Hgb, the physician at the bedside should treat the patient and clinical situation. A symptomatic patient with symptoms from anemia—whether with dyspnea, chest pain, or poor distal perfusion—likely warrants transfusion, as does the patient actively hemorrhaging with hemodynamic instability.

Restrictive vs. Liberal Transfusion Threshold

The AABB recommendations have their origins in several large clinical trials evaluating transfusion thresholds, specifically restrictive vs. liberal. Restrictive strategies typically have a threshold of 7 g/dL. Studies incorporating a restrictive threshold have been evaluated in various populations, including patients with sepsis, critically ill patients admitted to the ICU, cardiac surgery patients, orthopedic surgery patients, and trauma patients, with primary hypotheses that restrictive transfusion strategies were as safe as, or more safe than, liberal thresholds. Adverse effects of RBC transfusion were also evaluated, including infection, transfusion reaction, and immunomodulation (5,7,15,62–66). These adverse effects could impact patient morbidity and mortality.

The most commonly quoted study includes the landmark 1999 Transfusion Requirements in Critical Care (TRICC) trial, completed in patients admitted to the ICU who were euvolemic with Hgb <9 g/dL within 72 hours of admission. Patients were randomized to a restrictive (7 g/dL) or liberal transfusion (10 g/dL) strategy. No significant difference was found in all-cause mortality at 30 days, which was the primary outcome (restrictive 18.7%; liberal 23.3% [95% confidence interval {CI} –0.84–10.2%]; $p = 0.11$). Mortality during hospitalization was lower in the restrictive group, but no difference in ICU mortality was found (15). The Functional Outcomes in Cardiovascular Patients Undergoing Surgical Hip Fracture Repair (FOCUS) trial found no benefit to reducing mortality or improvement in ambulation with a restrictive (8 g/dL) vs. liberal (10g/dL) transfusion threshold. This study consisted of 2016 patients ≥50 years of age who were undergoing hip fracture surgery (67). The 2004 CRIT study, conducted in ICUs, found increased mortality with increasing number of RBC transfusions (5).

Other systematic reviews and meta-analyses have evaluated these thresholds, including the Cochrane database. A 2012 Cochrane review found restrictive transfusion strategies to be associated with reduced in-hospital mortality (risk ratio [RR] 0.77 [95% CI 0.62–0.95) but not 30-day mortality (RR 0.85 [95% CI 0.70–1.03]). The strategy did not affect duration of stay or functional recovery. The authors recommend use of a restrictive strategy, even with significant heterogeneity between trials, but the review warns about using restrictive strategy for patients with ACS (68). A second Cochrane review found restrictive strategies reduced infection (RR 0.76 [95% CI 0.60–0.97]) but did not affect mortality, cardiac events, stroke, or duration of stay (69).

A recently published meta-analysis found a restrictive threshold of 7 g/dL was associated with reduced in-hospital mortality (RR 0.74 [95% CI 0.60–0.92]), total mortality (RR 0.80 [95% CI 0.65–0.98]), rebleeding (RR 0.64 [95% CI 0.45–0.90]), ACS (RR 0.44 [95% CI 0.22–0.89]), pulmonary edema (RR 0.48 [95% CI 0.33–0.72]), and bacterial infections (RR 0.86 [95% CI 0.73–1.00]), with a number needed to treat of 33 to prevent 1 death. Less than 7 g/dL was not effective (70). A *British Medical Journal* meta-analysis evaluated 31 trials with 9813 patients. Similar to the Cochrane reviews, no difference in morbidity, mortality, or myocardial infarction was found when comparing liberal and restrictive transfusion strategies. However, they did find a reduced incidence of infection with a restrictive transfusion strategy (71).

Sepsis/Critically Ill

The care of the patient with sepsis underwent a revolution with early goal-directed therapy (EGDT) in 2001, in which blood transfusion was a central component of the protocol. The Surviving Sepsis Guidelines advised transfusion to Hgb of 10 g/dL or Hct of 30% during the first 6 hours if hypoperfusion persisted despite fluids and vasopressor support (72).

However, this threshold and ready transfusion in sepsis bundles was questioned because of the weak observational evidence. The Transfusion Requirements in Septic Shock (TRISS) trial enrolled approximately 1000 patients with septic shock and Hgb ≤9 g/dL who underwent randomization to 2 groups: 1 with a threshold of 7 g/dL and 1 with 9 g/dL. If patients met the threshold, 1 unit of leukoreduced RBCs was transfused. The investigators found that the primary outcome of death by 90 days did not differ between the groups (43% and 45%, respectively; RR 0.94 [95% CI 0.78–1.09]), and neither did the use of life support, mechanical ventilation, vasopressor support, or renal replacement therapy. The restrictive group had fewer units transfused. The authors suggested that avoiding unnecessary transfusions reduced the need for an expensive resource and reduced the risk of worsening infection or immune reaction (73).

The Protocolized Care for Early Septic Shock trial released in May 2014 compared original EGDT to a group with a less invasive protocol that required

transfusion for Hgb <7.5 g/dL and a group with treatment left to the discretion of the treating physician. The EGDT group underwent transfusion at a rate of 14.4%, approximately double that of the other groups. No difference in clinical outcomes was discovered (74). The Australasian Resuscitation in Sepsis Evaluation study compared EGDT with usual care. Again, the EGDT group underwent double the transfusion frequency when compared to the group undergoing usual care, with no difference in outcomes (75).

With data from these studies, a transfusion threshold of 7 g/dL in patients with septic shock is advised (66,73).

Gastrointestinal Bleeding

The studies evaluating transfusion threshold in patients with GI bleeding provide important information, because investigations were performed in patients with active hemorrhage. The TRICC and TRISS trials did not evaluate this subset of patients (15,73). The preeminent study by Villanueva et al. was a trial of adults with hematemesis or melena randomized to restrictive strategy (7 g/dL) vs. 9 g/dL. Of note, this trial excluded patients with minor bleeding or massive bleeding (defined by exsanguination) and patients with concern for ACS. All patients underwent endoscopy ≤6 hours after presentation. Interestingly, patients in the restrictive group had lower mortality rates compared to the liberal group (5% and 9%, respectively; $p = 0.02$). The rate of bleeding was also lower in the restrictive group (10% and 16%, respectively; $p = 0.01$), with fewer products transfused (76).

In the setting of nonvariceal bleeding, rebleeding was found to increase in patients transfused (23.6% vs. 11.3%; $p < 0.01$), and there was also an increase in 30-day mortality (6.8% vs. 3.7%; $p = 0.005$) (77). A second study conducted in the United Kingdom enrolled patients ≥18 years of age who had upper GI bleeding, randomizing patients to restrictive (8 g/dL) and liberal (10 g/dL) thresholds, with no difference in clinical outcomes (78). These findings in randomized trials are supported by a meta-analysis evaluating studies with restrictive vs. liberal transfusions for upper GI bleeding. This meta-analysis found restrictive transfusion groups had decreased death (odds ratio [OR] 0.26 [95% CI 0.03–2.10]; $p = 0.21$), shorter hospitalization (standard mean difference –0.17 [95% CI –0.30 to –0.04]; $p = 0.009$), and a significantly smaller amount of blood transfused (standard mean difference –0.74 [95% CI –1.15 to –0.32]; $p = 0.0005$) (79).

Why do transfusions potentially worsen outcomes in GI bleeding? It is hypothesized that transfusions counteract the splanchnic vasoconstriction caused in hypovolemia, increasing pressure in the splanchnic circulation and impairing clot formation. Transfusion may also alter coagulation properties. The concept of hemostatic resuscitation is paramount in these patients, with a restrictive transfusion strategy decreasing the number of transfusions and perhaps lowering mortality (76,77,79).

Restrictive transfusion in the setting of GI bleeding is recommended, with a transfusion threshold of 7 g/dL. Higher mortality, rebleeding, the need for intervention, and more frequent cardiac and pulmonary adverse effects are suggested by a meta-analysis in 2013 (79). Of note, these investigations of patients with GI bleeding are some of the only studies conducted in active bleeding, suggesting a transfusion threshold of 7 g/dL in active hemorrhage in patients with no symptoms of anemia with hemodynamic stability.

Acute Myocardial Ischemia

Transfusion in patients with myocardial ischemia, whether unstable angina, non-ST elevation myocardial infarction, or ST elevation myocardial infarction is a gray area, with much less investigation as compared to other conditions. Myocardial oxygen demands are high in the setting of ischemia, and during anemic states, oxygen delivery increases through stroke volume and heart rate, potentially worsening ischemia (80). On the other hand, circulatory overload and increased thrombogenicity may worsen with product transfusion (65,66).

The AABB currently does not identify a transfusion threshold in this population (66). Two small randomized trials with 155 patients compared transfusion triggers in patients with acute myocardial ischemia. One of these found increased congestive heart failure in patients transfused, but the other trial (with 110 patients) found rates of unscheduled revascularization within 30 days, death, or myocardial infarction of 10.9% in the liberal group and 25.5% in the restrictive group (risk difference 15% [95% CI 0.7–29.3%]). The authors suggested that a liberal transfusion strategy is associated with decreased cardiac events and death (81,82). Another study found cardiovascular mortality increased with Hgb levels <14 g/dL, and a meta-analysis found a restrictive threshold of 7 g/dL had a trend towards increased mortality in a subgroup of patients with ACS—but this was not statistically significant (13,14).

However, a review of 24,000 patients in the Global Use of Strategies To Open Occluded Arteries in Acute Coronary Syndromes, Platelet Glycoprotein IIb-IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy, and Platelet IIb/IIIa Antagonist for the Reduction of Acute Coronary Syndrome Events in a Global Organization Network trials found an increased risk of death in 30 days (adjusted hazard ratio 3.94 [95% CI 3.26–4.75]) in patients transfused in the setting of cardiac

disease/ischemia (83). A meta-analysis of 200,000 patients and 10 studies revealed increased all-cause mortality with a strategy of product transfusion (18.2%) when compared with no transfusion (10.2%; RR 2.91 [95% CI 2.46–3.44]; $p < 0.001$). The number needed to harm was 8. Transfusion was associated with a higher mortality rate independent of baseline Hgb, nadir Hgb, and change in Hgb during hospitalization (84).

The studies in this population all have multiple issues, including confounding factors, such as antiplatelet agents, varying transfusion thresholds, and differing primary outcomes. Unfortunately, the AABB does not make recommendations for this population (66). The meta-analysis provides the best data, with suggestions of risk with transfusion. Additional trials are needed in this population, but a restrictive threshold of 7 g/dL is likely safe if the patient is hemodynamically stable.

Trauma

Most physicians would agree that transfusion is required in the setting of acute, life-threatening trauma with massive hemorrhage. In fact, Hgb levels in active hemorrhage fail to accurately predict the actual RBC mass present, and anemia is often only discovered when non-RBC fluid replacement is provided. The Pragmatic Randomized Optimal Platelet and Plasma Ratios trial evaluated the ratio of blood products in massive transfusion. A ratio of 1:1:1 platelet to plasma to RBC transfusion strategy was associated with decreased death by exsanguination in the first 24 hours and increased chance of hemostasis on post hoc analysis when compared to a ratio of 1:1:2, but the primary outcome of 24-hour and 30-day mortality did not differ (85).

In major trauma victims not undergoing massive transfusion, RBC transfusion has been associated with increased mortality, lung injury, infection rates, multiple organ failure, and renal injury (86,87). Brachenridge et al. found an association between increased RBC transfusion >9.5 units with multiple organ dysfunction (OR 1.91) (86). A 2008 study evaluated the relationship between transfusion and patient outcomes, including mortality, infection rate, ICU admission, and duration of mechanical ventilation. Patients with transfusion had higher infection rate (34% vs. 9.4%), inpatient mortality (21.4% vs. 6.5%), ICU admission (74% vs. 26%), and duration of mechanical ventilation. Patients requiring transfusion had higher injury severity scales, lower Glasgow coma scale scores, and older age. When adjustments were made for these variables, infection was found to increase with increased transfusion (OR 2.8) with a slight increase in mortality (OR 1.05) (88). However, these associations present a challenge because of the injuries sustained and patient comorbidities. Fresh frozen plasma transfusion has also been associated with a greater risk of multiple organ failure, rather than RBCs, potentially confounding study results (87).

One trial has evaluated restrictive transfusion strategy for trauma patients using data from the TRICC trial. Investigators used a threshold of 7 g/dL (restrictive) and 10 g/dL (liberal). Patients included critically ill trauma patients with Hgb <9 g/dL, and investigators found that mortality, multiple organ dysfunction, and duration of stay were similar between the 2 groups (19).

At this time, resuscitation of the trauma patient with hemorrhage should be performed based on clinical status and not laboratory values. If the patient is in hemorrhagic shock, with acute hemorrhage and hemodynamic instability, transfusion is warranted. In acute trauma, a specific transfusion threshold is not warranted as a trigger for transfusion. Once the patient is hemodynamically stable, transfusion should be considered in the setting of anemic symptoms (e.g., chest pain, shortness of breath, or poor distal perfusion), with 1 unit of RBCs given at 1 time.

FUTURE DIRECTIONS

The central nervous system is dependent on a consistent metabolic supply of nutrients, including oxygen, because the brain and spinal cord have little anaerobic reserve and are not able to compensate for decreased oxygen delivery in the setting of anemia (89). Studies in patients with traumatic brain injuries and subarachnoid hemorrhages have suggested using a transfusion threshold of Hgb 8 to 9 g/dL, but more information is needed to develop true recommendations for transfusion (90,91). A subgroup analysis of the TRICC trial analyzed patients with moderate and severe head injury, with transfusion thresholds of 7 g/dL and 10 g/dL. Similar to previous findings and suggestions, no difference in mortality, multiple organ dysfunction, or duration of hospital stay were found. However, this was a retrospective subgroup analysis (92). A 2016 meta-analysis evaluated RBC transfusion in patients with traumatic brain injury and found no difference in mortality, with the transfusion threshold varying from Hgb 6 g/dL to 10 g/dL (93).

Defining transfusion thresholds for acute myocardial ischemia is also necessary, because the current studies to date have enrolled low sample sizes, used different thresholds, evaluated different outcomes, and have significant bias and heterogeneity (66,81–84). In reality, a definitive transfusion threshold for trauma is unlikely, because the majority of trauma patients are not managed based solely on laboratory markers.

Physicians should consider these transfusion thresholds and weigh the risks and benefits of transfusion. However, rather than relying on a laboratory level, the physician must evaluate the situation and patient. If the

patient is hemodynamically stable and asymptomatic, Hgb 7 g/dL is safe and is associated with a lower risk of reaction and infection. If the patient is hemodynamically unstable and anemic, transfusion may assist the provider in stabilizing the patient.

CONCLUSIONS

RBC transfusions have been used for many years for the treatment of anemia. Increased morbidity and mortality has been found with anemia in the setting of critical illness, trauma, surgery, and older age. The transfusion threshold of 10 g/dL has recently been questioned, and RBC transfusion is not without risks, which include transfusion reaction, infection, and potentially increased mortality. The AABB currently recommends a transfusion threshold of Hgb 7 g/dL. This evidence-based review evaluated the current literature of RBC transfusion impact on physiology, transfusion reactions, RBC product age, and transfusion thresholds. Studies evaluating transfusion are, for the most part, small in sample size, retrospective, and observational in nature, affecting their applicability. The majority of investigations have also been completed in critical care settings. Age of products transfused likely has no effect on products before 21 days of storage, but additional study is required. A Hgb level of 7 g/dL is safe in patients with critical illnesses, sepsis, gastrointestinal bleeding, and trauma. However, the provider at the bedside should evaluate the patient for symptoms associated with anemia and transfuse based on the risks and benefits.

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ARTICLE SUMMARY

1. Why is this topic important?

Transfusion of red blood cells is common, because anemia is associated with poor prognosis in various clinical settings, including critical illness. Anemia affects 90% of critically ill patients. Controversy exists surrounding the transfusion threshold and the age of products transfused.

2. What does this review attempt to show?

This review evaluates the current literature and controversy in transfusion of blood products, including transfusion thresholds and the effects of product age.

3. What are the key findings?

Transfusion of blood products should be viewed as donation of allogeneic tissue. The risk of transfusion includes infection and transfusion reaction, but these risks have decreased with recent practice. A standard transfusion threshold of 10 g/dL was previously used for transfusion. However, physiologic compensation occurs with chronic anemia, and transfusion can be associated with increased morbidity and mortality. Products stored for <21 days are safest. When considering transfusion, physicians should consider hemodynamic status and clinical setting. The American Association of Blood Banks recommends a transfusion threshold of 7 g/dL. A restrictive strategy with a transfusion threshold of 7 g/dL is safe and efficacious in the setting of hemodynamic stability and acute critical illness, sepsis and severe sepsis, gastrointestinal bleeding, and trauma. Additional research is required in acute myocardial ischemia and traumatic brain injury.

4. How is patient care impacted?

This review evaluates the current evidence for transfusions in critical illness. Recommendations are provided for transfusion of red blood cells in specific clinical settings.