ABSTRACT
Red blood cells are commonly administered to critically ill patients, yet the desired benefit of improving oxygen delivery and overall outcome may not be achieved in many scenarios. In addition, blood products are of limited supply and there are clear risks associated with blood transfusion. Despite this, studies show that almost half of all ICU patients receiving blood transfusions do so in the setting of stable anemia, suggesting that many critically ill patients in the ICU may receive unnecessary transfusions. Critical illnesses can lead to increased rates of anemia, even without active blood loss. The benefits of transfusion in these situations are unclear. Clear indications for blood transfusions, including uncontrolled hemorrhage, symptomatic anemia, and possibly acute coronary syndrome, are met in the minority of patients receiving red blood cell transfusions. This review discusses current evidence regarding the use of red blood cell transfusions in the ICU. Two major categories are examined, transfusion in patients noted to be anemic, but not clearly actively bleeding or symptomatic, and patients with aggressive bleeding who are critically ill or require massive transfusions.

INTRODUCTION
Anemia is a common phenomenon in the ICU, with approximately 30% of patients having a hemoglobin concentration less than 10 g/dL. In critically ill patients, the controversy to transfuse stems from a conflict of physiological principles and the results of randomized trials. As the oxygen carrier in blood, increased hemoglobin levels theoretically increase oxygen delivery and support the patient in shock. However, the benefit of transfusing liberally to a higher hemoglobin concentration in non-bleeding, anemic patients is unproven, and in certain cases may be harmful. Randomized trials have demonstrated that transfusing to a lower target may have lower complication rates and decreased mortality in particular groups of patients. It remains unclear if red cell transfusions themselves are the reason for worse clinical outcomes or the result of being critically ill with anemia.

CONSEQUENCES OF ANEMIA AND EFFECTS OF TRANSFUSION
Anemia has been clearly associated with poor outcomes in many instances, including with elderly patients, acute myocardial infarction, chronic kidney disease and acute respiratory failure. The causes of anemia in the critically ill are multifactorial and include acute blood loss [including recurrent phlebotomy], poor red cell production [from nutritional deficiencies, renal insufficiency, medications or decreased bone marrow response], hemolysis or sepsis. Transfusions of packed red blood cells are meant to increase oxygen delivery and reduce tissue hypoxia; however, multiple studies have failed to show improvement in oxygen delivery after transfusion. This may be due to various factors associated with stored blood, including low levels of 2,3-diphosphoglycerate (which shifts the oxygen dissociation curve to the left and decreases the ability of the transfused hemoglobin to unload oxygen in the tissues), structural problems with the stored RBCs which may lead to increased aggregation or hemolysis and the inflammatory response to the transfusion. Attempts to mitigate some of these causes of poor oxygen delivery by using “fresh” blood [mean age 6–12 days] versus older red cells [mean age 22 days] have not shown any improvements in outcome.

The risks for complications of transfusion are varied and increase with larger volume transfusion. These can vary from very minor [fever] to severe [anaphylaxis]. Due to extensive screening and testing, the risk of transferring a blood-borne infection [like HIV, hepatitis B or C] remains extremely low. Transfusion-related Lung Injury [TRALI] is an inflammatory-mediated non-cardiogenic pulmonary edema leading to hypoxia and potentially respiratory failure. It is the second leading cause [after anaphylaxis] of acute mortality due to blood transfusion. Coagulation abnormalities are also commonly seen from RBC transfusions due to direct dilutional effects [due to a lack of coagulation factors in RBC transfusions]. Furthermore, massive transfusions can cause potentially dangerous metabolic and electrolyte abnormalities. Packed RBC units contain citrate anticoagulant that induces hypocalemia from citrate binding to ionized calcium. Citrate itself metabolizes into bicarbonate and causes metabolic alkalosis, which can lead to hypokalemia. On the other hand,
hyperkalemia may also be noted as a result of the storage and lysis of blood products, with higher potassium levels observed when using blood stored for >12 days.6

**RBC TRANSFUSIONS IN STABLE CRITICALLY ILL PATIENTS**

Multiple studies have demonstrated increased mortality with RBC transfusion, yet rates of transfusion remain high. The CRIT Study described transfusion practices in the intensive care unit by examining 4892 critically ill patients.1 The mean pre-transfusion hemoglobin was 8.6 g/dL and the most common reason for transfusion was “low hemoglobin” [90% of all cases]. Other clinically relevant indications, such as active bleeding and hemodynamic instability, were seen in much fewer cases of transfusion (24 and 21%, respectively). In a more recent single-center study of 10,642 ICU patients in Canada, the rate of RBC transfusions during an ICU stay was noted to be 38.3%.7 These data describe a high, possibly excessive rate of blood cell transfusion in the ICU and suggest that defining appropriate transfusion thresholds is an important goal.

Prospective studies establishing appropriate thresholds for transfusing red blood cells in critically ill anemic patients have trended towards a more restrictive approach. The Transfusion Requirements in Critical Care (TRICC) trial randomized non-bleeding, anemic ICU patients without active heart disease to either a “liberal” (<9 mg/dL) or “restrictive” (<7 mg/dL) transfusion trigger. The restrictive strategy showed a trend towards mortality benefit in all patients, and demonstrated a statistically significant mortality benefit in pre-determined subgroups of younger patients (<55 years old) and in less critically ill patients (APACHE II score <20).8 After the publication of the TRICC trial, a hemoglobin of 7 g/dL became the widely accepted and recommended threshold for transfusion in non-bleeding critically ill patients, but questions regarding applicability relating to other subgroups persisted.9

In the Transfusion Requirements in Septic Shock (TRISS) study, patients with a diagnosis of septic shock were similarly assigned to two different transfusion thresholds. The comparison of transfusion thresholds of less than 7 g/dL [lower threshold] and less than 9 g/dL [higher threshold] did not show significant differences in 90-day mortality. In the subgroup analysis, patients with chronic cardiovascular disease also did not have a significant difference in relative risk of death by day 90.10 Another study examined patients with recent, treated acute upper-gastrointestinal bleeding, which demonstrated a higher probability of survival at six weeks if transfusions were administered at a lower threshold of 7 g/dL when compared to 9 g/dL.11 The primary outcome results from both trials are similar to the TRICC trial, which further support the use of a restrictive approach with blood transfusions. In both studies, patients with acute coronary syndrome (ACS) were excluded.

Anemia may worsen myocardial ischemia, induce arrhythmias, and increase infarct size during acute myocardial infarction. In patients with ACS or heart failure, anemia increases morbidity and mortality.12 In patients undergoing cardiac surgery, the Transfusion Requirements in Cardiac Surgery (TRICS III) trial demonstrated that a restrictive approach utilizing a hemoglobin threshold of 7.5 g/dL was noninferior to a liberal approach 9.5 g/dL. The primary outcome was a composite outcome of mortality, myocardial infarction, stroke, and new-onset renal failure requiring dialysis.13 Therefore, the 7.5 g/dL threshold is probably acceptable for post-cardiac surgery patients.

To our knowledge, there are no randomized trials that examine transfusion thresholds in patients with active cardiac ischemia or acute coronary syndrome. These patients have generally been excluded from randomized studies that compared transfusion thresholds. So while overall the trend with blood transfusions favors a lower threshold goal, there is no clear evidence that lower thresholds can be applied to patients with acute coronary syndrome.

**RBC TRANSFUSION IN UNSTABLE CRITICALLY ILL PATIENTS/MASSIVE TRANSFUSION**

The data discussed thus far pertain only to non-bleeding ICU patients with anemia. In the unstable, acutely hemorrhaging patient, large volumes of blood products may be necessary and restrictive transfusion triggers do not apply. The most commonly seen causes of severe acute bleeding stem from trauma, surgery, obstetrical bleeding and GI bleeding.14 Classic definitions of massive blood transfusion encompassed 10 units of PRBCs or a patient’s whole blood volume within 24 hours. Additional proposed definitions include three units of PRBCs within one hour15 and four units of total blood products within the first 30 minutes.16 The need to deliver blood products quickly and appropriately in the acute setting has led to the development of massive transfusion protocols.

There are several proposed methods to massive blood transfusion using different ratios of blood products. When large volumes of RBCs are delivered, dilutional coagulopathy can develop, therefore concurrent transfusion of plasma and platelets are recommended. The best available evidence for the optimal ratios of these various blood products has been described in trauma patients. The use of fresh frozen plasma (FFP), platelets, and PRBCs in a 1:1:1 ratio was compared to a group with 1:1:2 ratio in the Pragmatic, Randomized Optimal Platelet and Plasma Ratios (PROPPR) trial. There was no significant difference in mortality at 24 hours or 30 days between the two groups. However, there was better hemostasis achieved in the 1:1:1 group with fewer deaths by exsanguination within 24 hours.17 This ratio of blood products is most commonly advocated for use as part of massive transfusion protocols and is utilized at Rhode Island Hospital’s Level I Trauma Center.
There is far less evidence to target specific massive blood transfusion ratios in the non-trauma setting, for example, in medical bleeding patients. To our knowledge, there are no randomized studies examining massive transfusions in medical patients. However, a retrospective analysis of massive transfusion in non-trauma patients examined 30-day and 48-hour mortality. Patients were stratified to higher (>1:2) or lower (<1:2) ratios of FFP to RBC, and of platelets to RBC. The investigators found no associated difference in 30-day mortality with either groups of FFP to RBC or platelets to RBC ratios. In terms of shorter term, 48-hour mortality, there was an association of decreased mortality in the higher ratio of platelet to RBC group.\textsuperscript{18} Overall, further research is necessary to better define transfusion ratios in non-trauma bleeding patients and no specific recommendations regarding massive transfusions or ratios of blood products can be made in non-trauma actively bleeding patients.

As previously discussed, administering large amounts of blood products can cause significant derangements. In trauma care, the classic lethal triad includes hypothermia, acidosis, and coagulopathy. Although the sensitivity and specificity of each of these factors to prognosis are variable, the failure to correct physiological derangements can be detrimental.\textsuperscript{19} In severe trauma, restricting surgical interventions to the minimum necessary initially has led to the term “damage control surgery”\textsuperscript{20} (DCS). Similarly, the term “damage control resuscitation”\textsuperscript{21} (DCR) entails restricting of fluids, tolerating permissive hypotension, and administering specific ratios of blood products. Active patient rewarming, and massive transfusion protocol implementation are also part of these protocols.\textsuperscript{20} The combination of DCS and DCR has shown to be associated with an improvement in 30-day survival in trauma patients and remains a potentially promising strategy in other patient groups.\textsuperscript{21}

**CONCLUSIONS**

RBC transfusions remain a common intervention in the ICU; however, they may not result in the desired improved oxygen delivery or clinical outcomes. In the critically ill patient with exsanguination from traumatic injuries or uncontrolled bleeding, it is clear that blood products are necessary. However, in patients without active hemorrhage, the evidence suggests a more conservative approach with blood transfusions. Based on the current evidence, the transfusion threshold of 7.0 mg/dL is recommended for the majority of critically ill patients in the ICU. Patients with coronary artery disease or acute coronary syndrome may need a more liberal threshold; however, more research is necessary to elucidate the appropriate transfusion threshold for this population.

**References**


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