INVITED ARTICLE

Red Blood Cell Transfusion Thresholds in Critically Ill Patients

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Abstract

Anemia of multifactorial etiology is common among critically ill patients and several arbitrary transfusion thresholds have been proposed. Transfusion of red blood cells has been well established to increase morbidity and even mortality among critically ill patients. Several randomized controlled studies have evaluated the use of a restrictive compared to a more liberal transfusion strategy in the critically ill. A transfusion threshold of 7 g/dL appears to be generally safe, especially in the younger age group without significant comorbidities. Besides, a restrictive transfusion strategy reduces the incidence of transfusion-related complications. However, the decision to transfuse needs to be individualized depending on the clinical situation, balancing putative benefits against possible complications.

Keywords: Anemia, Blood transfusion, Critical illness, Hemoglobin

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Introduction

Transfusion of red blood cells is one of the age-old, iconic practices in medicine. Until recently, clinicians believed that a hemoglobin of 10 g/dL was an appropriate lower threshold among critically ill patients. Approximately 40% of patients admitted to the intensive care unit receive transfusion with red blood cells (RBCs), with the majority of transfusions for anemia unrelated to acute hemorrhage.[1] RBCs are transfused to augment oxygen delivery, based on the assumption that critically ill patients do not tolerate an oxygen debt. Although there is a clear association between anemia and increased mortality among critically ill patients,[2] it is unclear if correction of anemia with RBC transfusions improves survival in patients who are not actively bleeding.

Risks vs Benefits of RBC Transfusion

Oxygen bound to hemoglobin is carried by RBCs to the tissues; any drop in the hemoglobin level may potentially impair oxygen delivery. Compensatory mechanisms lead to an increase in cardiac output, resulting in increased oxygen delivery; besides, tissues respond with an increase in oxygen extraction. Healthy young adults may tolerate hemoglobin levels of up to 4 g/dL in the absence of hypovolemia.[3] However, in critically ill patients and in those with underlying comorbidities, compensatory mechanisms may be inefficient. The hemoglobin level at which compensatory mechanisms fail, leading to impaired oxygen consumption may be considered to the "critical" level at which RBC transfusions may be required. However, in a clinical setting, it is difficult to ascertain a critical level. Hence, arbitrary thresholds have been proposed for prophylactic RBC transfusion among critically ill patients.

Several complications are associated with transfusion that may offset any benefit derived from improved oxygen delivery. Transfusion-associated lung injury and circulatory overload may have a significant adverse impact among critically ill patients. Immunosuppression related to transfusion may increase the risk of bacterial infections, especially among postoperative patients.[4] The incidence of nosocomial infections may be related to the number of units transfused.[5] Clearly, any possible benefit from transfusion needs to be balanced against possible complications that may adversely impact outcomes. Table 1 summarizes the important randomized controlled trials that have compared hemoglobin thresholds in critically ill patients.

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Transfusion Threshold in General Critical Illness

Hemoglobin thresholds are commonly used in deciding the requirement for RBC transfusion. The clinical condition, age, or presence of comorbidities generally seem to influence clinician judgment regarding transfusion practice.[6] However, there is uncertainty regarding the point at which the benefits of improved oxygen carriage outweigh the risks associated with transfusion. The conventionally held dogma of RBC transfusion below a threshold of 10 g/dL was challenged by the Transfusion Requirements In Critical Care (TRICC) trial.[7] This multicentric, Canadian study enrolled 838 patients, who were randomized to a liberal or a restrictive transfusion strategy. In the liberal group, RBCs were transfused if the hemoglobin level dropped below 10 g/dL, with the maintenance of hemoglobin levels between 10 g/dL and 12 g/dL. In the restrictive group, the trigger for transfusion was a hemoglobin less than 7.0 g/dL, with the maintenance of hemoglobin concentration between 7 g/dL and 9 g/dL. All-cause mortality at 30 days, the primary outcome, was similar in both groups. Kaplan–Meir survival

Table 1: Important randomized controlled studies that have compared restrictive vs. liberal transfusion strategies among critically ill patients

Authors, year of publication	*Clinical setting*	*Restrictive trigger*	*Liberal trigger*	*Main findings*
Hébert et al. (1999)	General intensive care	Hb 7 g/dL	Hb 10 g/dL	No difference in all-cause mortality at 30 d. Significantly lower mortality in patients younger than 55 years and with lower baseline severity of illness with a restrictive strategy
Hajjar et al. (2010)	Postcardiac surgical	Hct 24%	Hct 30%	No difference in the composite primary outcome of 30-day all-cause mortality, ARDS, cardiogenic shock, and AKI requiring RRT
Carson et al. (2011)	Following hip surgery	Hb 8 g/dL	Hb 10 g/dL	No difference in mortality or the ability to walk a distance of 10 feet, unassisted, at 60 days
Walsh et al. (2013)	Patients of 55 years or more, requiring 4 or more days of ventilation	Hb 7 g/dL	Hb 9 g/dL	Trend towards lower mortality at 180 days with a restrictive strategy
Holst et al. (2014)	Septic shock	Hb 7 g/dL	Hb 9 g/dL	No difference in 90-day mortality. No difference in ischemic events, severe adverse reactions, or the requirement for life support

ARDS, acute respiratory distress syndrome; AKI, acute kidney injury; RRT, renal replacement therapy

curves during the 30-day period revealed significantly less mortality among patients who were less severely ill, with an APACHE II score of 20 or less, and for patients younger than 55 years. The in-hospital mortality, one of the secondary outcomes, was also lower in the restrictive group; however, there was no difference in mortality at 60 days. This landmark trial generated a considerable rethink on transfusion strategies in the critically ill and substantially influenced clinical practice.

A recent meta-analysis included 19,049 mixed medical-surgical patients from 37 randomized controlled trials.[8] Although different transfusion thresholds were used in individual studies, restrictive thresholds were commonly between 7 g/dL and 8 g/dL and liberal thresholds between 9 g/dL and 10 g/dL. Restrictive strategies reduced the probability of receiving a transfusion by 41%, with no difference in 30-day mortality, the primary endpoint. No difference was observed in the infection rates, functional recovery, and duration of intensive care unit or hospital stay. Furthermore, there was no increase in the risk in acute myocardial infarction among those who received a restricted transfusion strategy. Based on these studies, a restrictive transfusion strategy with a hemoglobin threshold of 7–8 g/dL may be recommended for most critically ill patients.

Thresholds for Specific Patient Populations

Septic Patients

Sepsis is defined as life-threatening organ dysfunction arising from a dysregulated host response to an infective illness.[9] Rivers et al. evaluated the efficacy of a "bundled" approach in patients with severe sepsis and septic shock.[10] One of the interventions in the bundle was RBC transfusion to a target of 10 g/dL if the central venous oxygen saturation remained less than 70%. Patients who received early goal-directed therapy (EGDT) had significantly better clinical outcomes. This led to the widespread use of a liberal transfusion strategy during the early phase of resuscitation in patients with septic shock. However, as this approach included a combination of several interventions, the effectiveness of individual components of the bundle was difficult to discern. Besides, the findings of the TRICC trial, which favored a restrictive transfusion strategy, was not available to the investigators.

The ProCESS, ARISE, and ProMISe trials compared EGDT to protocolized or usual care. The control arms of these studies used a lower hemoglobin threshold, with reduced transfusion requirements; however, there was no significant difference in clinical outcomes in patients who received protocolized or usual care.[11] These trials suggested that transfusion of RBCs aiming for higher hemoglobin thresholds may not improve outcomes during the early phase of sepsis resuscitation. The Transfusion Requirements in Septic Shock (TRISS) trial provided more robust evidence supporting a restrictive strategy.[12] This study included 998 patients with septic shock who were randomized to receive leukoreduced RBC transfusions at thresholds of 7–9 g/dL in the restrictive and liberal arms, respectively. During ICU stay, the restrictive group received a median of one unit of RBCs (interquartile range: 0–3), compared to four (interquartile range: 2–7) in the liberal group. The primary endpoint, the 90-day mortality, did not differ between groups. Furthermore, there was no difference in the incidence of ischemic events, severe adverse reactions, or the requirement for life support. In light of these studies, there is robust evidence to support a restrictive transfusion strategy in patients with septic shock.

Traumatic Brain Injury

Maintenance of adequate oxygen delivery is crucial in traumatic brain injury (TBI) as the brain is dependent on aerobic metabolism. Autoregulation protects the normal brain against ischemic insults within a limited range of cerebral perfusion pressures. The blood-brain barrier also prevents cerebral damage related to harmful systemic effects. However, these protective mechanisms are disrupted in TBI. A *post hoc* analysis of the TRICC trial included 67 patients with moderate to severe TBI. No mortality reduction was observed with a transfusion threshold of 10 g/dL compared to 7 g/dL among these patients. Robertson et al. conducted a randomized controlled trial to evaluate the effect of erythropoietin and transfusion thresholds of 7 vs 10 g/dL in patients with TBI.[13] No improvement in neurological outcomes was observed with either erythropoietin administration or the maintenance of a hemoglobin concentration of more than 10 g/dL. Furthermore, adverse events were more common when RBC transfusion was carried out at a threshold of 10 g/dL. Currently, there is no consensus on the optimal transfusion strategy in moderate to severe TBI. The Hemoglobin Transfusion Threshold in Traumatic Brain Injury Optimization (The HEMOTION trial) is recruiting patients with TBI and is scheduled to complete recruitment by 2021.

Patients with Acute Respiratory Failure on Mechanical Ventilation

Transfusion practices vary in patients with acute respiratory failure who require mechanical ventilation. It is unclear if a more liberal transfusion strategy may be appropriate with the widespread use and enhanced safety of leukodepleted blood and improved techniques of blood storage. The RELIEVE trial enrolled 100 patients, 55 years and older requiring 4 or more days of mechanical ventilation from six intensive care units in the United Kingdom.[14] Patients were randomized to maintain a hemoglobin level between 7.1 g/dL and 9.0 g/dL with a trigger of 7 g/dL for RBC transfusion or to maintain a hemoglobin level between 9.1 g/dL and 11.0 g/dL with a trigger of 9 g/dL. This strategy was followed for the duration of stay in the ICU after enrolment, or 14 days, whichever was longer. The study was meant to assess feasibility and not powered for outcomes. However, there was a trend toward lower 180-day mortality in the restrictive group (55 vs. 37%, CI: 0.44–1.05). The trend toward lower mortality with the restrictive strategy remained on *post hoc*-adjusted analysis that included age, gender, presence of ischemic heart disease, the APACHE II score, and non-neurological SOFA scores. Adequately powered randomized controlled trials are clearly required to confirm the potential benefits of a restrictive transfusion strategy in patients with acute respiratory failure who require a longer duration of mechanical ventilation.

Cardiovascular Disease

The myocardium has a limited capacity to utilize glycogen for the anerobic production of adenosine triphosphate. Besides, glycogen stores are rapidly depleted under ischemic conditions. In critically ill patients, coronary blood flow may be compromised due to hypotension and reduced organ perfusion; besides, the use of catecholamines to support the circulation may increase the oxygen demand. Anemia has been well established to cause increased mortality in acute myocardial infarction.[15] In a pilot randomized study, 110 patients with acute coronary syndrome or stable angina with a hemoglobin of less than 10 g/dL undergoing cardiac catheterization were enrolled. In the liberal group, red cells were transfused to maintain the hemoglobin level more than 10 g/dL, while in the restrictive arm, patients were transfused in the presence of symptoms due to anemia or to maintain the hemoglobin above 8 g/dL. The composite primary outcome of death, myocardial infarction, and emergency revascularization up to 30 days after randomization was lower in the liberal transfusion group although it did not reach statistical significance. A more definitive trial with adequate sample size is required to evaluate the appropriate transfusion strategy in acute coronary syndrome. Based on the limited evidence currently available, a higher transfusion threshold of 8 g/dL appears reasonable in patients with acute coronary syndrome.

Perioperative Patients

Anemia is generally considered to be associated with poor outcomes following cardiac surgery. However, acute kidney injury, infections, cardiac, respiratory, and neurological complications have been shown to be more common in patients who are transfused after cardiac surgery compared to those who do not receive transfusions in the postoperative period.[16] The Transfusion Requirements After Cardiac Surgery (TRACS) study randomized 502 patients who underwent cardiac surgery under cardiopulmonary bypass; RBCs were transfused to maintain a target hematocrit level of 30 vs 24%.[17] The composite primary outcome included 30-day all-cause mortality, acute respiratory distress syndrome, cardiogenic shock, and acute kidney injury requiring renal replacement therapy. The primary endpoint did not differ between groups; besides, the number of units transfused was found to be an independent predictor of death or the development of clinical complications at 30 days.

In a multicentric study involving 17 centers in the United Kingdom, 2007 patients were randomized to receive transfusions at a threshold hemoglobin level of 9 g/dL vs. 7.5 g/dL.[18] Patients were evaluated for a composite primary outcome including serious infection, or an acute ischemic event including stroke, acute myocardial infarction, gut ischemia, or acute kidney injury up to 3 months post-randomization. Patients randomized to the liberal group had nearly twice as many transfusions as those who were randomized to the restrictive group. The composite primary outcome was not significantly different between groups. The 90-d mortality, a secondary outcome, was higher with the restrictive strategy. Regardless of the transfusion strategy, the number of units transfused was an independent predictor of death or clinical complications at 30 days.

In a more recent, larger randomized controlled trial of cardiac surgical patients, a restrictive strategy (transfusion trigger 7.5 g/dL beginning with the induction of anesthesia) was compared to a more liberal strategy (transfusion trigger <9.5 g/dL in theater or ICU or <8.5 g/dL in the ward).[19] The composite primary outcome included all-cause mortality, acute myocardial infarction, stroke, or acute kidney injury requiring dialysis at hospital discharge or by day 28. A restrictive strategy was found to be noninferior to a more liberal strategy in this study. Based on the available evidence, a restrictive strategy with the maintenance of hemoglobin around 8 g/dL appears to be safe in patients undergoing cardiac surgery.

In the Functional Outcomes in Cardiovascular Patients Undergoing Surgical Hip Fracture Repair (FOCUS) trial, 2016 patients with cardiovascular risk factors, were assigned to a liberal compared to restrictive postoperative transfusion strategy following hip surgery.[20] Patients in the liberal group were transfused to maintain a hemoglobin of >10 g/dL; patients in the restrictive group were transfused if they developed symptoms of anemia or if the hemoglobin level dropped to less than 8 g/dL. There was no difference in mortality or the ability to walk unassisted to a distance of 10 feet at 60 days. No difference was noted in the incidence of in-hospital acute coronary syndrome or mortality at 3 years.

Although a recent meta-analysis suggested higher transfusion thresholds in perioperative patients,[21] and decisions to transfuse need individualization, a transfusion trigger of 8 g/dL seems appropriate following most types of surgery.

Conclusion

Anemia is common among critically ill patients and is usually of multifactorial origin; several arbitrary transfusion thresholds have been proposed. Blood transfusion has been well established to increase morbidity and even mortality among critically ill patients. Importantly, a restrictive strategy has not been found lead to harm in most clinical situations, compared to a more liberal approach. There is a strong body of evidence that suggests tolerance of lower levels of hemoglobin than conventionally believed in the critically ill. A transfusion threshold of 7 g/dL appears to be generally safe, especially in the younger age group without significant comorbidities. It is plausible that among patients with

acute coronary syndrome, a higher hemoglobin level may be required, considering the limited capacity of the myocardium to utilize glycogen for the anaerobic production of adenosine triphosphate. More robust evidence is required to evaluate transfusion requirements in this subgroup of patients. Transfusion decisions will clearly need to be individualized depending on the clinical situation, balancing putative benefits against possible complications.

References

1. Walsh TS, Garrioch M, Maciver C, Lee RJ, MacKirdy F, McClelland DB, et al. Red cell requirements for intensive care units adhering to evidence-based transfusion guidelines. Transfusion. 2004;44:1405–1411. doi:10.1111/j.1537-2995.2004.04085.x
2. Carson JL, Noveck H, Berlin JA, Gould SA. Mortality and morbidity in patients with very low postoperative Hb levels who decline blood transfusion. Transfusion. 2002;42:812–818. doi:10.1046/j.1537-2995.2002.00123.x
3. Weiskopf RB, Viele MK, Feiner J, Kelley S, Lieberman J, Noorani M, et al. Human cardiovascular and metabolic response to acute, severe isovolemic anemia. JAMA. 1998;279:217–221. doi:10.1001/jama.279.3.217
4. Hill GE, Frawley WH, Griffith KE, Forestner JE, Minei JP. Allogeneic blood transfusion increases the risk of postoperative bacterial infection: a meta-analysis. J Trauma. 2003;54:908–914. doi:10.1097/01.TA.0000022460.21283.53
5. Taylor RW, Manganaro L, O'Brien J, Trottier SJ, Parkar N, Veremakis C. Impact of allogenic packed red blood cell transfusion on nosocomial infection rates in the critically ill patient. Crit Care Med. 2002;30:2249–2254. doi:10.1097/00003246-200210000-00012
6. Corwin HL, Gettinger A, Pearl RG, Levy MM, Abraham E, MacIntyre NR, et al. The CRIT Study: Anemia and blood transfusion in the critically ill-current clinical practice in the United States. Crit Care Med. 2004;32:39–52. doi:10.1097/01.CCM.0000104112.34142.79
7. Hébert PC, Wells G, Blajchman MA, Marshall J, Martin C, Pagliarello G A, et al. Multicenter, Randomized, Controlled Clinical Trial of Transfusion Requirements in Critical Care. N Engl J Med. 1999;340:409–417.
8. Carson JL, Stanworth SJ, Alexander JH, Roubinian N, Fergusson DA, Triulzi DJ, et al. Clinical trials evaluating red blood cell transfusion thresholds: An updated systematic review and with additional focus on patients with cardiovascular disease. Am Heart J. 2018;200:96–101. doi:10.1016/j.ahj.2018.04.007
9. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016;315:801–810. doi:10.1001/jama.2016.0287
10. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med. 2001;345:1368–1377. doi:10.1056/NEJMoa010307
11. Napolitano LM. Anemia and Red Blood Cell Transfusion. Crit Care Clin. 2017;33:345–364. doi:10.1016/j.ccc.2016.12.011
12. Holst LB, Haase N, Wetterslev J, Wernerman J, Guttormsen AB, Karlsson S, et al. Lower versus Higher Hemoglobin Threshold for Transfusion in Septic Shock. N Engl J Med. 2014;371:1381–1391. doi:10.1056/NEJMoa1406617
13. Robertson CS, Hannay HJ, Yamal J-M, Gopinath S, Goodman JC, Tilley BC et al. Effect of erythropoietin and transfusion threshold on neurological recovery after traumatic brain injury: a randomized clinical trial. JAMA. 2014;312:36–47. doi:10.1001/jama.2014.6490
14. Walsh TS, Boyd JA, Watson D, Hope D, Lewis S, Krishan A, et al. Restrictive Versus Liberal Transfusion Strategies for Older Mechanically Ventilated Critically Ill Patients: A Randomized Pilot Trial. Crit Care Med. 2013;41:2354–2363. doi:10.1097/CCM.0b013e318291cce4
15. Salisbury AC, Amin AP, Reid KJ, Wang TY, Masoudi FA, Chan PS, et al. Hospital-acquired anemia and in-hospital mortality in patients with acute myocardial infarction. Am Heart J. 2011;162:300–309.e3. doi:10.1016/j.ahj.2011.05.021
16. Leal-Noval SR, Rincón-Ferrari MD, García-Curiel A, Herruzo-Avilés A, Camacho-Laraña P, Garnacho-Montero J, et al. Transfusion of blood components and postoperative infection in patients undergoing cardiac surgery. Chest. 2001;119:1461–1468. doi:10.1378/chest.119.5.1461
17. Hajjar LA, Vincent JL, Galas FR, Nakamura RE, Silva CM, Santos MH, et al. The TRACS Randomized Controlled Trial. JAMA. 2010;304:1559–1567. doi: 10.1001/jama.2010.1446.
18. Murphy GJ, Pike K, Rogers CA, Wordsworth S, Stokes EA, Angelini GD, et al. Liberal or restrictive transfusion after cardiac surgery. N Engl J Med. 2015;372(11):997–1008. doi: 10.1056/NEJMoa1403612.
19. C David Mazer, Richard P Whitlock, Dean A Fergusson, Judith Hall, Emilie Belley-Cote, Katherine Connolly, et al. Restrictive or Liberal Red-Cell Transfusion for Cardiac Surgery. N Engl J Med. 2017;377(22):2133–2144. doi:10.1056/NEJMoa1711818
20. Carson JL, Terrin ML, Noveck H, Sanders DW, Chaitman BR, Rhoads GG, et al. Liberal or restrictive transfusion in high-risk patients after hip surgery. N Engl J Med. 2011;365(26):2453–2462. doi: 10.1056/NEJMoa1012452. Epub 2011 Dec 14.
21. Fominskiy E, Putzu A, Monaco F, Scandroglio AM, Karaskov A, Galas FR, et al. Liberal transfusion strategy improves survival in perioperative but not in critically ill patients. A meta-analysis of randomised trials. Br J Anaesth. 2015 Oct;115(4):511–519. doi: 10.1093/bja/aev317.