JAMA Clinical Guidelines Synopsis

Transfusion of Red Blood Cells

Jason Alexander, MD; Adam S. Cifu, MD

GUIDELINE TITLE Blood Transfusion

DEVELOPER UK National Clinical Guideline Centre (NCGC)

RELEASE DATE November 15, 2015

FUNDING SOURCE National Institute for Health and Care Excellence (NICE)

TARGET POPULATION Adults older than 16 years and children aged 1 to 16 years who do not have special transfusion needs

MAJOR RECOMMENDATIONS

- Use restrictive red blood cell (RBC) transfusion hemoglobin thresholds (7 g/dL with a target of 7-9 g/dL) for patients who need RBC transfusions and who do not have major hemorrhage or acute coronary syndrome (ACS) or need regular blood transfusions for chronic anemia.
- For patients with ACS, consider an RBC transfusion hemoglobin threshold of 8 g/dL and a target of 8 to 10 g/dL.
- Consider setting individual thresholds and hemoglobin concentration targets for patients who need regular blood transfusions for chronic anemia.
- Consider single-unit transfusions for patients without active bleeding.
- Clinically reassess and check hemoglobin levels after each single-unit transfusion and give further transfusions if needed.

Summary of the Clinical Problem

Red blood cell transfusion is a common and potentially life-saving intervention, yet balancing the harms, benefits, scarcity of blood products, and cost remains complex. More than 13 million units of RBCs were transfused in the United States in 2013.[1] Transfusions are safe, with only 0.24% accompanied by an adverse reaction, and life-threatening transfusion reactions occur at a rate of only 15.1 per 1 million blood components transfused.[2] The average cost paid by hospitals to transfuse 1 RBC unit is $225.42, while the reimbursement rate from the Centers for Medicare & Medicaid Services is $194.86, resulting in a net loss to hospitals of 13.6%.

Editorial

Related article

Characteristics of the Guideline Source

The guideline was developed by the UK NCGC on behalf of NICE, which funded and supported creation of the guideline.[3] The NCGC assembled a guideline development group (GDG), a multidisciplinary team of health professionals, researchers, and lay members, to lead the process. All GDG members completed conflict-of-interest forms stating potential financial, business/professional, and intellectual conflicts at the start of guideline development and at all subsequent meetings. Members were required to partially or completely withdraw from the discussion if a declared conflict of interest was related to the review question being addressed. Following completion, the guideline underwent a peer review process for 6 weeks in which all comments from registered stakeholders were addressed and displayed on the NICE website (**Table**).

Evidence Base

The GDG identified 3 specific review questions related to RBC transfusions and completed a comprehensive literature review. Randomized clinical trials and systematic reviews were prioritized. Clinical questions were appraised using GRADE evidence profiles, and economic evidence profiles were generated to summarize cost and cost-effectiveness where available. All searches were updated prior to finalizing the guidelines to include the most current data. Final recommendations were reported in conjunction with standards set by the NICE guidelines manual, where strong recommendations were denoted by "offer" or "do not offer" and weaker recommendations were conveyed by "consider."[4]

Thirty-four studies pertaining to RBC transfusions involving 17 553 patients were analyzed by the GDG. Risk ratios comparing restrictive (generally defined as a transfusion threshold of 7-9 g/dL) and liberal (generally defined as a transfusion threshold of 8-10 g/dL) transfusion strategies from the meta-analysis associated with this guideline demonstrated no significant difference in 30-day mortality (risk ratio, 0.95; 95% CI, 0.77-1.17), new cardiac events (risk ratio, 1.00; 95% CI, 0.54-1.83), or infections (risk ratio, 0.92; 95% CI, 0.83-1.01) and no significant difference in length of hospital stay

Table. Guideline Rating

Rating Standard	Rating
Establishing transparency	Good
Management of conflict of interest in the guideline development group	Good
Guideline development group composition	Good
Clinical practice guideline–systematic review intersection	Good
Establishing evidence foundations and rating strength for each of the guideline recommendations	Good
Articulation of recommendations	Good
External review	Good
Updating	Good
Implementation issues	Fair

(risk ratio, −0.52; 95% CI, −1.11 to 0.06, where 0 favors neither a restrictive nor a liberal transfusion strategy and negative numbers favor a restrictive strategy). Restrictive strategies resulted in fewer patients receiving an RBC transfusion (risk ratio, 0.65; 95% CI, 0.59-0.73), and when transfusions were required, fewer units were administered (mean difference, −1.13; 95% CI, −1.67 to −0.59).

Higher transfusion targets were found to confer some benefit in patients with coronary artery disease. One small trial randomized 110 patients with ACS or stable angina undergoing catheterization to either a liberal (transfusion for hemoglobin <10 g/dL) or restrictive (transfusion for hemoglobin <8 g/dL) transfusion strategy and demonstrated reduced 30-day mortality (1.8% vs 13%; $P = .03$) with the liberal strategy.[5] A larger, more recent trial assessing postoperative management of anemia in 2003 patients following cardiac surgery also demonstrated higher mortality in patients receiving a restrictive (transfusion for hemoglobin <7.5 g/dL) vs a liberal (transfusion for hemoglobin <10 g/dL) transfusion strategy (4.2% vs 2.6%; hazard ratio, 1.64; 95% CI, 1.00-2.67; $P = .045$).[6]

Benefits and Harms

The guideline's recommendations could help reduce RBC transfusions that are unlikely to improve patient outcomes. Expected benefits include limiting exposure to transfusion-associated risks, reduced health care costs, and greater availability of blood products for situations in which transfusions are indicated. Extrapolating these recommendations to patients not covered by this guideline, including pregnant patients or patients with sickle cell disease, may be harmful. Significant uncertainty remains regarding how best to manage RBC transfusions in these patients.

Discussion

Anemia is commonly encountered in clinical practice. Establishing evidence-based guidance regarding transfusion is warranted. The available evidence suggests that for anemic patients without ACS or major hemorrhage, a higher hemoglobin goal confers no significant clinical benefit and an increased risk of harm. This finding held true even among critically ill patients. It is reasonable to conclude that a hemoglobin threshold of 7 g/dL for patients meeting the criteria for restrictive transfusion does not lead to increased mortality or cardiac events and can be utilized in clinical practice. Patients with coronary artery disease should be managed with a higher hemoglobin goal.

The recommendations of the GDG differ somewhat from those released by the American Association of Blood Banks (AABB).[7] Following a systematic review of 31 randomized clinical trials that included 12 587 patients, the AABB advises the same restrictive transfusion threshold of 7 g/dL for hemodynamically stable patients; however, this does not include patients undergoing cardiac or orthopedic surgery or who have preexisting cardiovascular disease, in whom a transfusion threshold of 8 g/dL is recommended. Furthermore, because of insufficient evidence, the AABB gives no guidance for transfusion thresholds in patients with ACS or chronic transfusion-dependent anemia or hematology/oncology patients with severe thrombocytopenia who are at risk of bleeding. These differences highlight the need for well-designed trials that include these patient populations.

Areas in Need of Future Study or Ongoing Research

There is limited evidence regarding optimal transfusion thresholds and targets in patients with chronic cardiovascular disease, although there is some suggestion liberal transfusion strategies may be of benefit for these patients. A post hoc analysis of patients with ischemic coronary disease in the TRICC trial[8] as well as an a priori subgroup of patients with cardiovascular disease in critically ill patients with septic shock[9] both showed benefits when hemoglobin thresholds for transfusion were higher, but well-designed studies will need to be performed before any significant conclusions can be made. These findings suggest that transfusions threshold and goals may vary according to patient population, and studies of these populations are warranted.

Related Guidelines and Other Resources

NICE guideline on acute upper gastrointestinal tract bleeding
https://www.nice.org.uk/guidance/cg141/evidence

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EDITORIAL

AABB Red Blood Cell Transfusion Guidelines
Something for Almost Everyone

Mark H. Yazer, MD; Darrell J. Triulzi, MD

In this issue of *JAMA*, Carson and colleagues[1] provide an important update to the red blood cell (RBC) transfusion guidelines developed in 2012 by the AABB (formerly the American Association of Blood Banks). The authors based the current guidelines and recommendations on the results of 31 randomized clinical trials (RCTs) performed in a variety of different clinical settings involving more than 12 500 patients who were randomized to receive transfusion triggered by either a hemoglobin concentration of less than 7 g/dL to 8 g/dL (restrictive strategy referred to as the conservative strategy) or a hemoglobin concentration of less than 9 g/dL to 10 g/dL (liberal strategy). The evaluation used the Grading of Recommendations Assessment, Development and Evaluation methods and appropriately considered only RCTs, thereby avoiding the invariable confounding present in observational studies examining blood transfusion. In aggregate, the analysis convincingly demonstrated that adverse consequences (mortality and major morbidity) were not more common among patients assigned to a conservative transfusion strategy compared with a liberal one. Thus, the authors of this guideline recommend a conservative transfusion policy.

Related articles

Unlike the previous 2012 version of the RBC transfusion guidelines that recommended overlapping hemoglobin concentration triggers of 7 g/dL to 8 g/dL for most inpatients,[2] these updated guidelines recommend 2 distinct tiers of hemoglobin triggers for RBC transfusions: hemoglobin concentration of less than 7 g/dL for stable, adult inpatients including those in the intensive care unit, and hemoglobin concentration of less than 8 g/dL for a select group of postsurgery patients or those with preexisting cardiac disease. The 2-tiered approach acknowledges the current state of the evidence and also provides support for making more individualized transfusion decisions.

In the intensive care unit setting, transfusions are given to reduce the risk of major morbidity and mortality, and such outcomes can be achieved using either a conservative hemoglobin concentration transfusion trigger of less than 7 g/dL or a liberal transfusion strategy. However, for some patients, such as those undergoing hip replacement surgery, functional recovery has traditionally represented the primary rationale for transfusion, and this outcome can also be achieved using either a conservative hemoglobin concentration transfusion trigger of less than 8 g/dL or a liberal strategy. Thus, although both critically ill patients and patients who had major orthopedic surgery were safely managed with a conservative transfusion strategy, the study design tested a hemoglobin concentration transfusion trigger of 7 g/dL for critically ill patients and a hemoglobin transfusion trigger of 8 g/dL for patients undergoing orthopedic surgery, with different primary outcomes. Thus, there is no definitive evidence of the safety of using a hemoglobin transfusion trigger of 7 g/dL in some specific patient populations (ie, those undergoing orthopedic surgery and cardiac surgery); hence, the guidelines offer 2 RBC transfusion thresholds.

Whether patients undergoing cardiac surgery or older patients (>65 years) undergoing major orthopedic surgery can be safely managed at a hemoglobin transfusion trigger of 7 g/dL is not known. In an RCT of 2007 patients undergoing cardiac surgery who were randomized to receive transfusion at a hemoglobin level of less than 7.5 g/dL compared with less than 9 g/dL, there was no difference in the primary composite outcome of serious morbid events. However, in a predefined secondary analysis, 90-day mortality was higher in the group assigned to the conservative trigger (4.2%) compared with the liberal trigger (2.6%) (hazard ratio, 1.67 [95% CI, 1.00-2.67]; $P = .045$).[3] Similarly, in a study of 2016 patients who underwent surgical hip repair, no difference was observed in the primary composite end point of mortality or functional recovery among those randomized to transfusion for a hemoglobin level of less than 8 g/dL vs less than 10 g/dL. However, in a predefined secondary analysis, acute myocardial infarction was observed more commonly in those assigned to the conservative trigger (3.8%) compared with the liberal trigger (2.3%) (odds ratio, 0.76 [99% CI, 0.30-1.19]).[4] These secondary analyses do not provide sufficient data for drawing definitive conclusions, but the observations among patients assigned to the restrictive intervention groups suggest that a hemoglobin transfusion trigger of less than 7 g/dL may not be safe for all patients. More will be learned following the completion of a trial[5] currently testing a hemoglobin trigger of less than 7 g/dL for patients undergoing cardiac surgery.

The AABB's current 2-tier recommendation for RBC transfusion specifically excludes certain patient populations such as those with acute coronary syndromes. Even though the Grading of Recommendations Assessment, Development and Evaluation methods did not permit a specific guideline recommendation for these patients based on the current evidence, these patients still need to be managed when they present to the hospital. Two small pilot RCTs,[6,7] the Myocardial Ischemia and Transfusion and the Conservative vs Liberal Red Cell Transfusion in Acute Myocardial Infarction, evaluated conservative (at hemoglobin level of 8 g/dL) vs liberal (at hemoglobin level of 10 g/dL) transfusion thresholds in a total of 155 patients who were experiencing acute cardiac events. An unanticipated large effect was observed with better survival among patients assigned to a liberal vs conservative transfu-

sion strategy (1.8% mortality vs 13.0% mortality, respectively). These preliminary data need to be confirmed in a properly powered RCT and serve as an important reminder that a conservative RBC transfusion strategy may not be safe for all patients. While awaiting confirmation of the results of these pilot studies, it seems prudent to consider a liberal approach to transfusion for patients with acute coronary syndromes.

Good clinical practice dictates that the decision to transfuse should not be solely based on the hemoglobin level. Clinical factors, availability of alternative therapies, and patient preferences should be considered. That does not mean that guidelines provided by Carson and colleagues[1] are without value, but rather that guidelines reflect general recommendations that apply to most patients in most situations. A major limitation of these guidelines is that they are based on hemoglobin level as the transfusion trigger. Hemoglobin is a measure of the oxygen carrying capacity of blood, but does not indicate tissue oxygen delivery or the level of tissue oxygenation. Perhaps direct measurement of tissue oxygenation using noninvasive methods[8-11] or plasma markers, such as base deficit,[8] lactate,[10] or other biomarkers, coupled with the measurement of hemoglobin level will provide a more clinically relevant indication of the need for RBC transfusion. Hopefully, future RBC transfusion guidelines will be able to incorporate rigorous evidence from more physiological markers that assess tissue oxygenation.

The promulgation of conservative RBC transfusion guidelines raises the following questions: How low can the transfusion threshold go? Should withholding transfusion to even lower hemoglobin values (eg, <6 g/dL) be studied? There would likely be diminishing returns in doing so and that the risks of serious morbidity and mortality at that hemoglobin threshold will likely outweigh the risks of transfusion. The current body of RCTs that served to inform these guidelines indicates that patients in the liberal transfusion intervention groups did not experience higher rates of morbidity or mortality compared with those in the restrictive transfusion groups, despite receiving many more RBC units.[12] Thus, prior observational reports of serious adverse outcomes associated with RBC transfusion have not been borne out by the RCT data.[12] It may follow that the risks of transfusing a unit of RBCs is lower than previously thought and would not justify accepting excessive risks at very low hemoglobin values. Along this line, even though the safety of the hemoglobin transfusion trigger of less than 7 g/dL has been amply demonstrated in patients in intensive care units, this transfusion trigger should not be extended to any other patient population unless its safety has been demonstrated in properly conducted studies.

This updated version of the AABB guidelines also includes for the first time a recommendation of how long RBC units should be stored before transfusion. Among 13 evaluated RCTs that collectively enrolled 5515 patients, no clinical differences (including 30-day mortality, myocardial infarction, cerebrovascular accident, rebleeding, pneumonia, or thromboembolism) were found among those assigned to receive longer-storage RBCs compared with RBC units with shorter-storage duration. Thus, the AABB did not recommend making any changes in the usual blood bank practice of issuing the oldest RBCs first.

This recommendation reveals science as it should evolve; the hypothesis that the receipt of standard issue RBC units could lead to higher morbidity and mortality was suggested by an observational study of patients undergoing cardiac surgery.[13] When this concept was tested in well-designed RCTs, the original hypothesis was shown not to be valid in patients undergoing cardiac surgery, critically ill patients, or premature neonatal patients.[14] Rather than the duration of storage, the indication for RBC transfusion remains the more pertinent clinical question.

These new guidelines from the AABB represent medicine at its best in that they are evidence based, derived from RCTs, reflect important clinical perspectives, and are definitive for conditions in which data are substantial, but provide greater flexibility for conditions in which data are less certain.

ARTICLE INFORMATION

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COMMENTARY

Transfusion Thresholds in the ICU: Is the Pendulum Swinging Back?

Aaron B. Holley, MD | November 03, 2016

Transfusion Thresholds

For many years, the findings of the Transfusion Requirements in Critical Care (TRICC) trial guided packed red blood cell (pRBC) administration in the intensive care unit (ICU).[1] This multicenter, randomized controlled trial (RCT) compared a conservative transfusion threshold (7.0 g/dL hemoglobin [Hgb]) with a liberal threshold (10.0 g/dL Hgb). The investigators found that outcomes were equivalent or improved (in certain subgroups) among the conservative approach group. Those with clinically significant cardiac disease showed equivalent outcomes, but the authors advised caution when applying their data to this subgroup.

The TRICC trial was designed to study only stable patients in the ICU. For specific subgroups, however, transfusion thresholds are more controversial. For example, let's consider patients with stable coronary artery disease (CAD) and acute myocardial infarction (AMI). I blogged about this back in 2013,[2] after a meta-analysis[3] and subsequent *ACP Journal Club* article[4] addressed transfusion and AMI. The meta-analysis included only one RCT, with a small sample. Otherwise, all studies were observational. The authors concluded that pRBC transfusion during AMI may actually be harmful, but acknowledged that a large trial was desperately needed.

Transition Thresholds in Patient Subgroups

Transfusion thresholds in stable CAD remain controversial. For many years, I extrapolated data from the TRICC trial and said that a threshold of 7 g/dL was appropriate for these patients. In TRICC, there were approximately 200 patients with stable CAD, and in subgroup analysis, there was no difference in outcomes between the two arms.[1]

Other subgroups must be considered. In 2001, Rivers and colleagues[5] showed that transfusion to a Hgb value of 10 mg/dL was beneficial for patients with septic shock. In fairness, transfusion to 10 mg/dL was one of many interventions for these patients, so any benefit attributable to this practice is difficult to quantify. Regardless, many authors recommended a target of 10 mg/dL for patients with septic shock.[6]

Another setting is acute bleeding. A recent RCT looked at trigger thresholds in patients with acute upper gastrointestinal bleeding.[7] The researchers found that a conservative threshold (7 g/dL Hgb) reduced mortality compared with a liberal threshold (9 g/dL Hgb). One caveat is that all patients in this study received gastroscopy and intervention to the site of bleeding (as appropriate) within 6 hours of presentation.

Updated Transfusion Guidelines

This month, *JAMA* published the American Association of Blood Banks (AABB) guidelines for pRBC transfusion and storage.[8] These guidelines update those published by the same organization in 2012.[9] The authors summarized findings across multiple subgroups using data published between 1950 and May 2016.

The guidelines include several interesting findings. Not surprisingly, they concluded that a conservative threshold of 7 g/dL was not associated with increased 30-day mortality. Although the absolute difference in mortality was 3 fewer deaths per 1000 patients, the 95% confidence interval ranged from 15 fewer deaths to 18 more deaths. There were no differences in outcomes other than mortality. Surprisingly, they did not find an increased risk for infection among patients in the liberal threshold group. This was in contrast to the results of a previously published meta-analysis.[9,10]

The guidelines compared Hgb levels of 7 g/dL and 8-9 g/dL and found no statistical difference between the groups. The caveat is that the patients studied were different. Most patients in the studies of 7 g/dL Hgb were critically ill, whereas those in the 8- to 9-g/dL Hgb groups were heterogeneous in degree of illness. Of note, patients undergoing orthopedic or cardiac surgery and those with stable CAD tended to be in the 8- to 9-g/dL Hgb groups. Even though an indirect comparison showed no difference, the AABB recommends a transfusion threshold of 7 g/dL for critically ill and hospitalized patients but 8 mg/dL for patients undergoing orthopedic/cardiac surgery and those with stable

CAD.

The AABB was unable to provide recommendations for patients with AMI. Despite calls for a large RCT to answer this important clinical question,[2-4] only one additional RCT was performed between 2012 and 2016.[11] Data from this trial were combined with those from a small randomized trial published in 2011.[12] These studies included a total of 155 patients, with one showing increased mortality in the liberal threshold group and the other showing the opposite. Both studies reached statistical significance. When combined they showed a trend toward a benefit using a liberal threshold.

The AABB authors note that several other societies have issued recommendations for transfusion thresholds in the setting of AMI or acute coronary syndrome (ACS). These threshold recommendations are inconsistent and range from 7 g/dL to 10 g/dL Hgb.[8] The editorial that accompanied the AABB guidelines in this month's *JAMA* advocated for a liberal strategy in the setting of AMI/ACS.[13]

A Caution About Extrapolation

The editorial also mentions the "pendulum swing" that I refer to in the title of this commentary. Although it's true that the safety of a conservative Hgb threshold has been established for specific groups, it's also true that RCTs do not show adverse effects from pRBC transfusion. We know that such adverse effects exist (they are summarized nicely in the beginning of the guidelines), but they occur infrequently. Some patient groups are harmed by a conservative strategy, so clinicians should be careful not to extrapolate data beyond the specific population studied. Conservative strategies have become very popular, but if pRBC transfusions are not as harmful as once thought, the risk/benefit tradeoff is slightly shifted.

I plan to do as the guidelines say and use a threshold of 7 g/dL in the ICU, or 8 g/dL if the patient has a history of CAD. If there is evidence of ACS, I will go a little higher. Although the guidelines don't address patients with sepsis, I rarely push these patients to 10 g/dL, particularly because subsequent trials haven't confirmed the mortality benefit originally seen with early goal-directed therapy.[14] I don't have the guts to restrict my patients with active gastrointestinal bleeding—another group that isn't addressed by the AABB. We don't always obtain upper endoscopies within 6 hours of presentation. I would be careful in applying data from this trial to your patients if your facility doesn't reliably provide early intervention.

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Clinical Practice Guidelines From the AABB
Red Blood Cell Transfusion Thresholds and Storage

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IMPORTANCE More than 100 million units of blood are collected worldwide each year, yet the indication for red blood cell (RBC) transfusion and the optimal length of RBC storage prior to transfusion are uncertain.

OBJECTIVE To provide recommendations for the target hemoglobin level for RBC transfusion among hospitalized adult patients who are hemodynamically stable and the length of time RBCs should be stored prior to transfusion.

EVIDENCE REVIEW Reference librarians conducted a literature search for randomized clinical trials (RCTs) evaluating hemoglobin thresholds for RBC transfusion (1950-May 2016) and RBC storage duration (1948-May 2016) without language restrictions. The results were summarized using the Grading of Recommendations Assessment, Development and Evaluation method. For RBC transfusion thresholds, 31 RCTs included 12 587 participants and compared restrictive thresholds (transfusion not indicated until the hemoglobin level is 7-8 g/dL) with liberal thresholds (transfusion not indicated until the hemoglobin level is 9-10 g/dL). The summary estimates across trials demonstrated that restrictive RBC transfusion thresholds were not associated with higher rates of adverse clinical outcomes, including 30-day mortality, myocardial infarction, cerebrovascular accident, rebleeding, pneumonia, or thromboembolism. For RBC storage duration, 13 RCTs included 5515 participants randomly allocated to receive fresher blood or standard-issue blood. These RCTs demonstrated that fresher blood did not improve clinical outcomes.

FINDINGS It is good practice to consider the hemoglobin level, the overall clinical context, patient preferences, and alternative therapies when making transfusion decisions regarding an individual patient. Recommendation 1: a restrictive RBC transfusion threshold in which the transfusion is not indicated until the hemoglobin level is 7 g/dL is recommended for hospitalized adult patients who are hemodynamically stable, including critically ill patients, rather than when the hemoglobin level is 10 g/dL (strong recommendation, moderate quality evidence). A restrictive RBC transfusion threshold of 8 g/dL is recommended for patients undergoing orthopedic surgery, cardiac surgery, and those with preexisting cardiovascular disease (strong recommendation, moderate quality evidence). The restrictive transfusion threshold of 7 g/dL is likely comparable with 8 g/dL, but RCT evidence is not available for all patient categories. These recommendations do not apply to patients with acute coronary syndrome, severe thrombocytopenia (patients treated for hematological or oncological reasons who are at risk of bleeding), and chronic transfusion-dependent anemia (not recommended due to insufficient evidence). Recommendation 2: patients, including neonates, should receive RBC units selected at any point within their licensed dating period (standard issue) rather than limiting patients to transfusion of only fresh (storage length: <10 days) RBC units (strong recommendation, moderate quality evidence).

CONCLUSIONS AND RELEVANCE Research in RBC transfusion medicine has significantly advanced the science in recent years and provides high-quality evidence to inform guidelines. A restrictive transfusion threshold is safe in most clinical settings and the current blood banking practices of using standard-issue blood should be continued.

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More than 100 million units of blood are collected worldwide each year,[1] and approximately 13 million red blood cell (RBC) units are collected in the United States.[2] Despite previously published guidelines,[3-7] there remains substantial variation in the practice of transfusing patients. Physicians often use hemoglobin level to decide when to transfuse,[8] although some guidelines[9,10] maintain that transfusion should be given for symptoms of anemia and not solely based on hemoglobin level.

Transfusion practices for RBCs should be designed to optimize clinical outcomes and to avoid transfusions that are not clinically indicated. Despite the risk of transfusion-transmitted infections and noninfectious adverse events, such as transfusion-related acute lung injury and transfusion-associated circulatory overload, RBC transfusion is relatively safe (**Table 1**). However, transfusing RBCs unnecessarily exposes patients to increased risk and costs without benefit. Consequently, transfusing RBCs at higher hemoglobin thresholds (ie, a liberal transfusion strategy) should be used only if a liberal strategy will improve the outcomes that are important to patients.

In addition to transfusion reactions and infectious risks associated with RBC transfusions, it has been suggested that an RBC storage lesion may result in adverse outcomes. Units of RBCs can be stored up to 42 days. The RBCs stored for longer periods have decreased ability to deliver oxygen due to decreased levels of 2,3-diphsophoglycerate, decreased nitric oxide metabolism, alterations of the RBC membrane leading to increased rigidity, and increased RBC endothelial adherence.[19,20] In addition, the storage medium may contain increased levels of free hemoglobin, iron, potassium, and inflammatory mediators that may lead to deleterious consequences.[19,21] Furthermore, observational studies[22-24] suggested that RBCs stored longer than 2 weeks may be associated with increased morbidity and mortality; however, the data were conflicting.[25-27] These considerations raise the possibility that transfusion medicine services should preferentially provide fresher RBCs for transfusion compared with standard issue RBCs.

In 2012, the AABB (formerly known as the American Association of Blood Banks) published RBC transfusion guidelines based on 19 randomized clinical trials (RCTs) that included 6264 patients.[28] Many of those RCTs were small (median, 120 patients; range, 22 to 2016 patients) and had high risk of bias. During the past 4 years, the number of patients enrolled in RBC transfusion RCTs has more than doubled, and many studies have incorporated methods to minimize the risk of bias and enrolled populations of patients receiving frequent blood transfusions. Therefore, it is timely to reexamine the evidence and provide updated guidance to the medical community.

Thirteen RCTs have evaluated the effect of RBC storage duration of transfused RBCs on patient outcomes (7 since 2012).[29-41] However, there is currently no formal guidance on the optimal length of RBC storage prior to transfusion.

Methods

These guidelines provide recommendations for (1) the clinicians caring for hospitalized adult patients who are hemodynamically stable and candidates for RBC transfusions, and (2) the transfusion medicine services responsible for storing and providing RBCs. The AABB commissioned and funded the development of these guidelines through the AABB clinical transfusion medicine committee. In addition, the board of directors charged the committee to recruit experts with an interest in RBC transfusion from other professional organizations.

Guideline Development Process

A committee of experts was assembled. Most of the experts were current or former members of the AABB clinical transfusion medicine committee (J.L.C., N.M.H., B.J.G., C.S.C., M.K.F., T.G., L.M.K., G.R., J.D.R., and A.A.R.T.). There also were experts appointed by professional organizations as subject matter experts (American Association for the Surgery of Trauma: J.B.H.; Society of Critical Care Medicine: L.J.K.; American College of Cardiology: S.V.R.; American Society of Anesthesiologists: A.S.; and American Society of Hematology: T.G.). The committee also included a patient representative (N.P.). Eight of the physicians were pathologists or hematologists (most with subspecialty expertise in transfusion medicine). The other physicians included an anesthesiologist, cardiologist, internist, critical care medicine physician, trauma or acute care surgeon, and a Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodologist (G.G.).

The committee members had no substantial conflicts of interest (as defined by the AABB conflict of interest policy[42]). Pursuant to the conflict of interest policy, individual members were required to disclose actual and apparent financial, professional, or personal conflicts. Two members were authors on trials included in the systematic review on transfusion thresholds (J.L.C. and S.V.R.), 1 authored a systematic review of transfusion thresholds (J.L.C.), 2 were authors on trials of RBC storage duration (J.L.C. and N.M.H.), and 2 were authors on systematic reviews of RBC storage duration (G.G. and N.M.H.). One member (J.L.C.) was excused when voting on transfusion thresholds for patients with acute myocardial infarction due to his role as principal investigator on a pending grant proposal.

Evidence Review and Grading

Systematic Review

The guidelines were developed based on separately published updated systematic reviews of the literature on transfusion thresholds[43] and RBC storage duration.[44] We performed literature searches of RCTs evaluating transfusion thresholds from 1950 through May 2016 and the storage duration of transfused RBCs from 1948 through May 2016.[43] The systematic review included RCTs in which the transfusion groups were assigned on the basis of a clear transfusion trigger or threshold, which was described as hemoglobin or hematocrit level that had to be reached before a RBC transfusion was administered. Trials of patients treated surgically, medically, or both were included as well as those involving adults or children (but not neonates). For the RBC storage systematic review, the included RCTs enrolled patients admitted to the hospital requiring a RBC transfusion and compared fresher vs standard issue RBC transfusions.[44] The term *standard issue* used in these guidelines is defined as units selected at any point within their licensed dating period, but only a small proportion of RBC units transfused were stored for 36 days to 42 days.

The primary outcome in both systematic reviews was mortality (30-day mortality for transfusion thresholds and a composite of the longest follow-up provided in each trial, including 30 days, 90 days, and in-hospital mortality for RBC storage duration). Secondary outcomes for transfusion thresholds included morbidity (eg, nonfatal myocardial infarction, pulmonary edema or congestive heart failure, stroke, thromboembolism, renal failure, infection, rebleeding, or mental confusion); the proportion of patients transfused with allogeneic RBCs, autologous

Table 1. Approximate Risk Per-Unit Transfusion of Red Blood Cells (RBCs)

Adverse Event	Approximate Risk Per-Unit Transfusion of RBCs
Febrile reaction[11]	1:60[a]
Transfusion-associated circulatory overload[12,13]	1:100[b]
Allergic reaction[14]	1:250
Transfusion-related acute lung injury[15]	1:12 000
Hepatitis C virus infection[16]	1:1 149 000
Hepatitis B virus infection[17]	1:1 208 000 to 1:843 000[c]
Human immunodeficiency virus infection[16]	1:1 467 000
Fatal hemolysis[18]	1:1 972 000

[a] Estimated to be 1:91 with prestorage leukoreduction and 1:46 with poststorage leukoreduction.

[b] Indicates the estimated risk per recipient rather than unit.

[c] The estimate is variable depending on the length of the infectious period.

RBCs, or both; hemoglobin levels (the timing of measurement varied among trials); and the number of RBC units transfused. For RBC storage, the secondary outcomes included adverse events and nosocomial infection. The systematic reviews only included RCTs because observational studies evaluating the effect of transfusion are especially prone to confounding by indication and are likely to yield biased results.[45,46]

Each RCT was assessed for the risk of bias for sequence generation, allocation concealment, blinding, and incomplete outcome data using the methods recommended by Cochrane (for transfusion threshold review)[47] and a modified risk of bias assessment tool (for storage duration).[48] Statistical heterogeneity was assessed using both I^2 and χ^2 tests.[47] Existing criteria provided guidance for making inferences regarding subgroup effects.[49] All analyses were performed using Review Manager (RevMan) version 5.2 (Cochrane Collaboration). The relative risks (RRs) and the corresponding 95% CIs were calculated for each trial using random-effects models.[50]

Rating Quality of Evidence

The GRADE method[51,52] was used to develop these guidelines (eAppendix in the Supplement). Evidence profiles were prepared that displayed data in terms of benefits and harms for the most important outcomes. The profiles also were the basis for decisions regarding the rating down of quality for risk of bias, lack of consistency, lack of directness, lack of precision, and possible publication bias. The overall quality of evidence for each outcome was assessed for the systematic review on transfusion thresholds (J.L.C. and Simon Stanworth, MD, DPhil) and for the systematic review on RBC storage (Paul Alexander, PhD, G.G., and N.M.H.). The committee reviewed these ratings and made its final quality ratings and determined the strength of the recommendations during an in-person meeting.

Committee Values and Preferences

With respect to transfusion thresholds, the committee made its recommendations based on the assumption that patients would highly value avoiding the rare but potentially serious adverse effects associated with RBC transfusion. Moreover, the committee placed value on resource conservation related to RBC transfusion. Therefore, when the evidence suggested no harms from withholding transfusion, the committee was prepared to make a strong recommendation for a restrictive threshold. When evidence regarding harms was uncertain, the committee elected not to make a recommendation.

With respect to RBC storage duration, the committee placed a high value on feasibility and resource use considerations for RBC transfusion. Therefore, if evidence suggested no harms in using standard-issue blood, the committee was prepared to make a strong recommendation for continuing with standard practice. The recommendations were voted and then the first (J.L.C.) and last (A.A.R.T.) authors prepared the draft guideline document, which was modified and approved by all committee members and the AABB clinical transfusion medicine committee. Subsequently, the AABB board of directors reviewed and approved the guidelines.

Good Clinical Practice Statement

When deciding to transfuse an individual patient, it is good practice to consider not only the hemoglobin level, but the overall clinical context and alternative therapies to transfusion. Variables to take into consideration include the rate of decline in hemoglobin level, intravascular volume status, shortness of breath, exercise tolerance, lightheadedness, chest pain thought to be cardiac in origin, hypotension or tachycardia unresponsive to fluid challenge, and patient preferences. This practice guideline is not intended as an absolute standard and will not apply to all individual transfusion decisions.

Recommendations

First Recommendation

The AABB recommends a restrictive RBC transfusion threshold in which the transfusion is not indicated until the hemoglobin level is 7 g/dL for hospitalized adult patients who are hemodynamically stable, including critically ill patients, rather than a liberal threshold when the hemoglobin level is 10 g/dL (strong recommendation, moderate quality evidence). For patients undergoing orthopedic surgery or cardiac surgery and those with preexisting cardiovascular disease, the AABB recommends a restrictive RBC transfusion threshold (hemoglobin level of 8 g/dL; strong recommendation, moderate quality evidence). The restrictive hemoglobin transfusion threshold of 7 g/dL is likely comparable with 8 g/dL, but RCT evidence is not available for all patient categories. These recommendations apply to all but the following conditions for which the evidence is insufficient for any recommendation: acute coronary syndrome, severe thrombocytopenia (patients treated for hematological or oncological disorders who at risk of bleeding), and chronic transfusion-dependent anemia.

Evidence Summary

A total of 12 587 patients were enrolled in 31 eligible trials.[53-86] Ten trials were conducted in patients undergoing orthopedic surgery, 6 trials included patients treated in critical care units, 5 trials

were conducted in patients undergoing cardiac surgery, 5 trials were conducted in patients with gastrointestinal bleeding, 2 trials included patients with acute coronary syndrome, 2 trials included patients with leukemia or hematological malignancies, and 1 trial was conducted in patients undergoing vascular surgery. The restrictive RBC transfusion protocols commonly used a hemoglobin transfusion threshold of 7 g/dL or 8 g/dL, and liberal protocols used a hemoglobin transfusion threshold of 9 g/dL to 10 g/dL.

The association of restrictive transfusion protocols on 7 outcomes reported in the trials appears in **Table 2**. The primary outcome of 30-day mortality was reported in 23 of 30 RCTs.[53-56,58,60,61,63,64,68-72,74-76,78,79,84-87] In the restrictive transfusion group, the absolute difference in 30-day mortality was 3 fewer deaths per 1000 patients (95% CI, 15 fewer deaths to 18 more deaths per 1000). The quality assessment found no serious risk of bias, inconsistency, indirectness, or publication bias. The overall quality of evidence was moderate for 30-day mortality because the imprecision was judged as serious in that there could be up to 18 more deaths per 1000 in the restrictive transfusion group.

For all other outcomes evaluated, there was no evidence to suggest that patients were harmed by restrictive transfusion protocols, although the quality of the evidence was low for the outcomes of congestive heart failure and rebleeding. In addition, liberal transfusion was not found to be associated with an increased risk of infection as had been previously found in a prior meta-analysis.[88] There was also no difference in the other assessed outcomes (ability to walk, multiple measures of function, fatigue, and length of hospital stay) in the systematic review.[43]

The 30-day mortality for the trials that used a restrictive hemoglobin transfusion threshold of less than 8 g/dL to 9 g/dL (n = 4772) was compared with those using a restrictive hemoglobin transfusion threshold of less than 7 g/dL (n = 5765). The RRs were similar, and there is no evidence that these 2 threshold groups are statistically different (χ^2_1 = 0.34, P = .56, I^2 = 0%; **Figure 1**). However, the clinical settings were different. Most of the trials with the restrictive hemoglobin transfusion threshold of less than 7 g/dL were performed in critical care settings, whereas the clinical settings were more varied with the hemoglobin transfusion threshold of less than 8 g/dL to 9 g/dL.

The subgroup analyses for 30-day mortality by clinical setting[43] did not demonstrate statistically significant evidence to support differences in the subgroups; however, 30-day mortality was significantly lower with the restrictive transfusion threshold than the liberal transfusion threshold in patients with gastrointestinal bleeding (RR, 0.65; 95% CI, 0.43-0.97). Two small trials included 154 patients with acute coronary syndrome. There were 9 deaths with the restrictive transfusion threshold and 2 deaths with the liberal transfusion threshold (RR, 3.88 [95% CI, 0.83-18.13]; P = .08, I^2 = 67.6% for the comparison of these 2 small trials). The results for myocardial infarctions from these 2 trials (n = 154 patients) were then compared with the other 29 trials in all other clinical settings (P = .08, I^2 = 67.6%).

Rationale for Recommendation

The AABB recommendation to use a hemoglobin transfusion threshold of 7 g/dL to 8 g/dL for most hospitalized adult patients who are hemodynamically stable rather than a hemoglobin transfusion threshold of 9 g/dL to 10 g/dL is based on consistent evidence from multiple large RCTs performed in various clinical settings in more than 12 000 patients. With the possible exception of patients with acute myocardial infarction, no data suggest that a restrictive transfusion threshold is harmful compared with a liberal transfusion threshold. A restrictive transfusion threshold approach is associated with reductions in blood use, associated expense, and uncommon but potentially serious adverse events.

The AABB recommends using a restrictive hemoglobin transfusion threshold of 7 g/dL for hospitalized adult patients who are hemodynamically stable, including critically ill patients, but a hemoglobin transfusion threshold of 8 g/dL for patients undergoing orthopedic or cardiac surgery and for those with underlying cardiovascular disease. The reason for the different thresholds is that the RCTs performed in the later groups of patients used a hemoglobin transfusion threshold of 8 g/dL and not a threshold of 7 g/dL. The committee suspects that those patients might tolerate a hemoglobin transfusion threshold of 7 g/dL because the trials using a restrictive threshold of 7 g/dL were performed in critically ill patients compared with other trials with a threshold of 8 g/dL and less critically ill patients. However, this has not been assessed in RCTs and it is possible that functional recovery (in patients undergoing orthopedic surgery) or myocardial infarction rates (in patients undergoing cardiac surgery or with chronic cardiovascular disease) could be adversely affected by a hemoglobin transfusion threshold of 7 g/dL or higher even if mortality is not. An ongoing large trial among patients undergoing cardiac surgery is using a restrictive hemoglobin transfusion threshold of 7.5 g/dL and may provide a definitive answer.[89]

As in the AABB's previous guideline,[28] the committee chose not to recommend for or against a liberal or restrictive transfusion threshold in patients with acute coronary syndrome. There are 2 trials with a total of 154 patients that showed a trend toward a lower risk of death when the liberal transfusion threshold was used.[56,61] This finding is consistent with experimental studies in canines,[90-92] in an observational study of patients undergoing surgery with underlying cardiovascular disease,[93] and in the prespecified a priori hypothesis and direction in the 2 small trials.[56,61] However, small RCTs are known to be unreliable; in fact, the size of the effect observed was larger than anticipated, but the results were not statistically significant.

The AABB also did not make a recommendation for a transfusion threshold in patients treated for hematological or oncological disorders and for those with severe thrombocytopenia who are at risk of bleeding or for those with chronic transfusion–dependent anemia. Red blood cells have been shown to increase platelet responsiveness,[94] especially at lower platelet counts.[95] Data from animal experiments[96] and normal volunteers suggest that anemia increases the bleeding time, even with as little as a 15% decrease in hemoglobin level.[97] For this reason, some clinicians advocate for higher hemoglobin thresholds in patients with severe thrombocytopenia who are at increased risk of bleeding. Except for 2 pilot studies,[86,98] RCTs comparing RBC transfusion thresholds with bleeding as an end point have yet to be performed. Similarly, there have not been RCTs performed in patients with chronic transfusion–dependent anemia. The risks and benefits (ie, improved function, less fatigue) are different for patients receiving chronic transfusions outside the hospital than hospitalized patients in acute care settings.

Second Recommendation

The AABB recommends that patients, including neonates, should receive RBC units selected at any point within their licensed dating

Table 2. Evidence for the Association Between Hemoglobin Transfusion Thresholds and Clinical Outcomes in Hospitalized Adult Patients Who Are Hemodynamically Stable and in Need of a Red Blood Cell Transfusion[a]

	Quality Assessment[b]					No./Total (%) of Patients by Hemoglobin Transfusion Threshold		Effect		
No. of RCTs	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Restrictive (7-8 g/dL)	Liberal (9-10 g/dL)	Relative Risk (95% CI)	Absolute Risk (95% CI)	Quality of RCTs
Primary Outcome: 30-d Mortality										
23	Not serious	Not serious	Not serious	Serious[c]	None detected	470/5221 (9.0)	497/5316 (9.3)	0.97 (0.81-1.16)	3 fewer deaths per 1000 (15 fewer deaths to 18 more per 1000)	Moderate
Secondary Outcomes										
Myocardial Infarction (MI)										
16	Not serious	Not serious	Not serious	Not serious	None detected	78/4156 (1.9)	69/4147 (1.7)	1.08 (0.74-1.60)	1 more MI per 1000 (4 fewer MIs to 10 more per 1000)	High
Pulmonary Edema (PE) or Congestive Heart Failure (CHF)										
12	Serious[d]	Not serious	Not serious	Serious[e]	None detected	87/3132 (2.8)	114/3125 (3.6)	0.78 (0.45-1.35)	8 fewer PEs or CHFs per 1000 (13 more PEs or CHFs to 20 fewer per 1000)	Low
Stroke or Cerebrovascular Accident (CA)										
13	Not serious	Not serious	Not serious	Not serious	None detected	49/3675 (1.3)	62/3668 (1.7)	0.78 (0.53-1.14)	4 fewer strokes or CAs per 1000 (2 more strokes or CAs to 8 fewer per 1000)	High
Rebleeding										
6	Not serious	Serious[f]	Not serious	Serious[g]	None detected	215/1489 (14.4)	264/1619 (16.3)	0.75 (0.51-1.10)	41 fewer events per 1000 (16 more events to 80 fewer per 1000)	Low
Pneumonia										
14	Not serious	Not serious	Not serious	Not serious	None detected	239/3140 (7.6)	256/3137 (8.2)	0.94 (0.80-1.11)	5 fewer cases of pneumonia per 1000 (9 more cases to 16 fewer per 1000)	High
Thromboembolism										
10	Not serious	Not serious	Not serious	Not serious	None detected	16/2010 (0.8)	21/2009 (1.0)	0.77 (0.41-1.45)	2 fewer thromboembolisms per 1000 (5 more thromboembolisms to 6 fewer per 1000)	High

Abbreviation: RCT, randomized clinical trial.

[a] This Table addresses the question of whether hospitalized adult patients who are hemodynamically stable should receive a restrictive transfusion approach with a hemoglobin threshold of 7 g/dL to 8 g/dL rather than a liberal transfusion approach with a hemoglobin threshold of 9 g/dL to 10 g/dL.

[b] Evaluates the risk of bias, inconsistency based on the heterogeneity among trials, indirectness based on the generalizability of the results, imprecision based on the width of the 95% CIs, and publication bias based on some trials not being published. The Grading of Recommendations Assessment, Development and Evaluation method (eAppendix in the Supplement) was used.

[c] Could be 1 more death to up to 18 more deaths per 1000 in the restrictive transfusion group.

[d] The blinding of participants and personnel was impossible. The blinding of outcome assessment was inconsistent between trials.

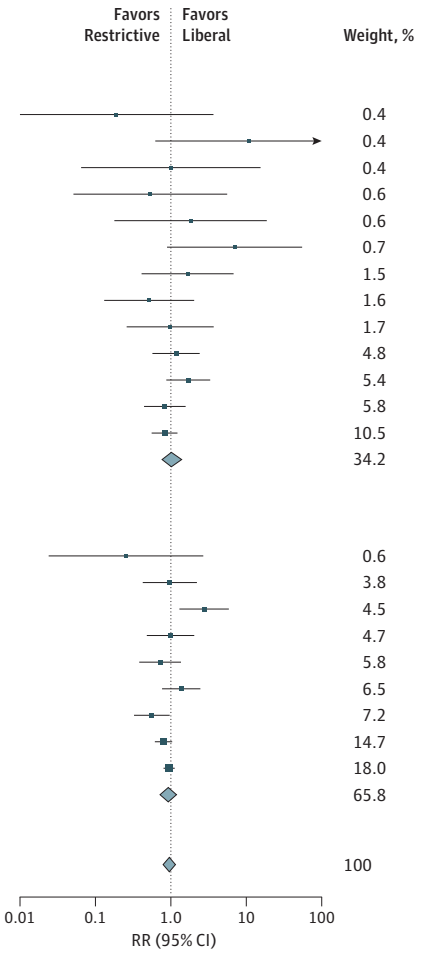
[e] Studies had moderately wide 95% CIs.

[f] I^2 = 58% and P = .04.

[g] Could be 1 more event to up to 16 more events per 1000 in patients in the restrictive transfusion group.

Figure 1. Comparison of 30-Day Mortality Using Restrictive vs Liberal Hemoglobin Transfusion Thresholds in Randomized Clinical Trials

Source	Restrictive Transfusion Threshold No. of Deaths	Restrictive Transfusion Threshold Total No.	Liberal Transfusion Threshold No. of Deaths	Liberal Transfusion Threshold Total No.	RR (95% CI)	Weight, %
Restrictive threshold, hemoglobin <8 to 9 g/dL						
Lotke et al,[75] 1999	0	62	0	65	Not estimable	
Blair et al,[53] 1986	0	26	2	24	0.19 (0.01-3.67)	0.4
Foss et al,[63] 2009	5	60	0	60	11.00 (0.62-194.63)	0.4
Carson et al,[58] 1998	1	42	1	42	1.00 (0.06-15.47)	0.4
Webert et al,[86] 2008	1	29	2	31	0.53 (0.05-5.58)	0.6
Cooper et al,[61] 2011	2	23	1	21	1.83 (0.18-18.70)	0.6
Carson et al,[56] 2013	7	55	1	55	7.00 (0.89-55.01)	0.7
Parker,[78] 2013	5	100	3	100	1.67 (0.41-6.79)	1.5
Bracey et al,[54] 1999	3	215	6	222	0.52 (0.13-2.04)	1.6
Bush et al,[55] 1997	4	50	4	49	0.98 (0.26-3.70)	1.7
Hajjar et al,[68] 2010	15	249	13	253	1.17 (0.57-2.41)	4.8
Gregersen et al,[64] 2015	21	144	12	140	1.70 (0.87-3.32)	5.4
Jairath et al,[72] 2015	14	257	25	382	0.83 (0.44-1.57)	5.8
Carson et al,[60] 2011	43	1009	52	1007	0.83 (0.56-1.22)	10.5
Subtotal	121	2321	122	2451	1.05 (0.78-1.40)	34.2
Heterogeneity: $\tau^2 = 0.02$; $\chi^2_{12} = 13.14$; $P = .36$; $I^2 = 9\%$						
Tests for overall effect: z score = 0.31; $P = .76$						
Restrictive threshold, hemoglobin <7 g/dL						
DeZern et al,[87] 2016	1	59	2	30	0.25 (0.02-2.69)	0.6
Hébert et al,[70] 1995	8	33	9	36	0.97 (0.42-2.22)	3.8
de Almeida et al,[79] 2015	23	101	8	97	2.76 (1.30-5.87)	4.5
Lacroix et al,[74] 2007	14	320	14	317	0.99 (0.48-2.04)	4.7
Walsh et al,[85] 2013	12	51	16	49	0.72 (0.38-1.36)	5.8
Murphy et al,[76] 2015	26	1000	19	1003	1.37 (0.76-2.46)	6.5
Villanueva et al,[84] 2013	19	416	34	417	0.56 (0.32-0.97)	7.2
Hébert et al,[69] 1999	78	418	98	420	0.80 (0.61-1.04)	14.7
Holst et al,[71] 2014	168	502	175	496	0.95 (0.80-1.13)	18.0
Subtotal	349	2900	375	2865	0.94 (0.74-1.19)	65.8
Heterogeneity: $\tau^2 = 0.05$; $\chi^2_8 = 16.09$; $P = .04$; $I^2 = 50\%$						
Tests for overall effect: z score = 0.53; $P = .59$						
Overall	470	5221	497	5316	0.97 (0.81-1.16)	100
Heterogeneity: $\tau^2 = 0.04$; $\chi^2_{21} = 29.75$; $P = .10$; $I^2 = 29\%$						
Tests for overall effect: z score = 0.29; $P = .77$						
Tests for subgroup differences: $\chi^2_1 = 0.34$; $P = .56$; $I^2 = 0\%$						



The size of the data markers indicates the weight of the trial; RR, relative risk. Trials published after 2012 have been published since the prior AABB transfusion guidelines.

period (standard issue) rather than limiting patients to transfusion of only fresh (storage length: <10 days) RBC units (strong recommendation, moderate quality evidence).

Evidence Summary

There were 13 trials meeting the inclusion criteria.[29-41] The trials included neonates and infants with very low birth weights and children and adults; most patients had an acute critical illness or surgical hemorrhage. The trials that were conducted in North America, South America, Europe, Australia, and Africa compared fresher blood with standard-issue blood; however, the storage duration of the standard-issue blood varied between the trials. In the 2 primary trials involving neonates, the mean storage durations at the time of transfusion were 1.6 days and 5.1 days for fresher RBCs compared with 9.0 days and 14.1 days for standard issue RBCs.[31,35] The storage duration of the transfused RBCs in the trials of adults ranged from a median of 4 days (mean, 12.1 days) for fresher RBCs compared with a median of 19 days (mean, 28 days) for standard issue RBCs.

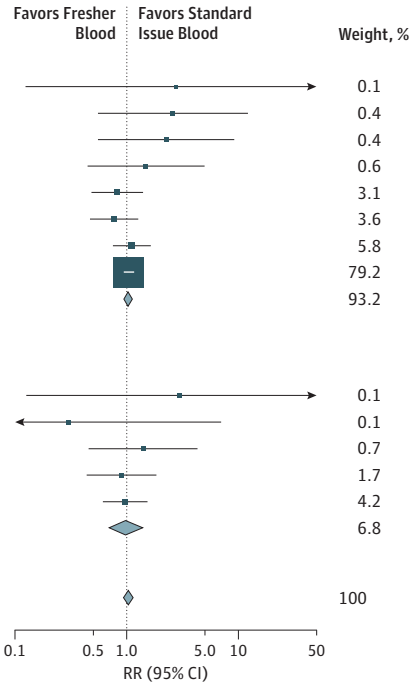
A forest plot shows no evidence that transfusion of fresher RBCs is superior to standard issue RBCs for the outcome of mortality (RR, 1.04; 95% CI, 0.95-1.14) with similar estimates in both adults and infants (**Figure 2**). The association of RBC storage duration on 3 clinical outcomes reported in the trials appears in **Table 3**. The absolute difference in 30-day mortality was 4 more deaths per 1000 with fresher blood (95% CI, 5 fewer deaths to 14 more deaths per 1000).

The RCT quality assessment found no serious risk of bias, inconsistency, indirectness, or publication bias. The overall quality of RCT evidence was moderate for 30-day mortality because the 95% CI included an important decrease in deaths with fresher blood.

There was no evidence to suggest that patients had more adverse events by receiving standard issue RBCs; however, the quality of the evidence was low. For nosocomial infections, there was a higher risk of infection among patients receiving fresher RBCs with an absolute difference of 43 more nosocomial infections per 1000 patients transfused (95% CI, 1 more nosocomial infection to 86 more nosocomial infections per 1000); however, the quality of evidence was low (Table 3).

Figure 2. Association Between Fresher vs Standard-Issue Blood and Mortality in Adults, Neonates, Infants, and Children in Randomized Clinical Trials

Source	Fresher Blood No. of Deaths	Fresher Blood Total No.	Standard Issue Blood No. of Deaths	Standard Issue Blood Total No.	RR (95% CI)	Weight, %
Adults						
Bennett-Guerrero et al,[33] 2009	1	12	0	11	2.77 (0.12-61.65)	0.1
Aubron et al,[34] 2012	5	25	2	26	2.60 (0.55-12.19)	0.4
Schulman et al,[30] 2002	4	8	2	9	2.25 (0.55-9.17)	0.4
Hébert et al,[32] 2005	5	26	4	31	1.49 (0.45-4.98)	0.6
Steiner et al,[41] 2015	23	538	29	560	0.83 (0.48-1.41)	3.1
Kor et al,[37] 2012	17	50	22	50	0.77 (0.47-1.27)	3.6
Heddle et al,[36] 2012	35	309	61	601	1.12 (0.75-1.65)	5.8
Lacroix et al,[40] 2015	448	1211	430	1219	1.05 (0.94-1.17)	79.2
Subtotal	538	2179	550	2507	1.04 (0.95-1.15)	93.2
Heterogeneity: $\tau^2=0$; $\chi^2_7=5.47$; $P=.60$; $I^2=0\%$						
Tests for overall effect: z score = 0.85; $P=.40$						
Neonates, Infants, and Children						
Dhabangi et al,[38] 2013	1	37	0	37	3.00 (0.13-71.34)	0.1
Strauss et al,[29] 1996	0	21	1	19	0.30 (0.01-7.02)	0.1
Dhabangi et al,[39] 2015	7	143	5	143	1.40 (0.45-4.31)	0.7
Fernandes da Cunha et al,[31] 2005	9	26	10	26	0.90 (0.44-1.85)	1.7
Fergusson et al,[35] 2012	30	188	31	189	0.97 (0.61-1.54)	4.2
Subtotal	47	415	47	414	0.99 (0.69-1.42)	6.8
Heterogeneity: $\tau^2=0$; $\chi^2_4=1.46$; $P=.83$; $I^2=0\%$						
Tests for overall effect: z score = 0.06; $P=.96$						
Overall	585	2594	597	2921	1.04 (0.95-1.14)	100
Heterogeneity: $\tau^2=0$; $\chi^2_{12}=7.00$; $P=.86$; $I^2=0\%$						
Tests for overall effect: z score = 0.81; $P=.42$						
Tests for subgroup differences: $\chi^2_1=0.08$; $P=.78$; $I^2=0\%$						



Mortality is based on a composite of the longest follow-up period provided in each trial including 30 days, 90 days, and in-hospital mortality. The size of the data markers indicates the weight of the trial; RR, relative risk.

Rationale for Recommendation

There was consistent evidence in multiple large RCTs performed in a variety of clinical settings among more than 5000 patients. We found no evidence that the transfusion of fresher blood decreased mortality compared with standard-issue blood. However, the RBC storage duration trials did not evaluate patients undergoing a massive or exchange transfusion; neonates and children with underlying renal disease at higher risk of hyperkalemia; patients undergoing intrauterine transfusions; or patients with hemoglobinopathies requiring chronic transfusion support.

Discussion

Transfusion is a common therapeutic intervention for which there is considerable variation in clinical practice.[3-7] If clinicians continue to adopt a restrictive transfusion strategy of 7 g/dL to 8 g/dL, the number of RBC transfusions would continue to decrease.[43] In addition, standard practice should be to initiate a transfusion with 1 unit of blood rather than 2 units. This would have potentially important implications for the use of blood transfusions and minimize the risks of infectious and noninfectious complications.

The average duration of RBC storage in the United States is 17.9 days, although storage duration differs among hospitals and patient populations.[99] Only a small proportion of patients in the RCTs would have been exposed to RBCs near the storage expiration (35-42 days), which could be the products most affected by storage lesions. The standard issue RBC storage duration for neonates is often less than for adult patients; this was true in the 2 primary trials involving neonates.[31,35] However, there was no overall signal that standard issue RBCs were harmful and the overall RR estimate trended toward a lower mortality when standard issue RBCs were used for transfusions.

Limitations

These guidelines are based on the best, but nevertheless incomplete, evidence available today. The hemoglobin transfusion thresholds that have been assessed may not be optimal. The use of hemoglobin transfusion thresholds may be an imperfect surrogate for oxygen delivery. The trials evaluating RBC storage duration have not assessed the effect of long-term storage (near the 42-day expiration for RBC units stored with additive solution); hence, the application of the AABB's recommendation to centers with predominately RBCs stored for longer than 35 days is unknown.

Comparison With Other Guidelines

Red blood cell transfusion guidelines[100-107] from 8 societies during the past 5 years addressed hemoglobin transfusion thresholds. Each of the guidelines recommended a restrictive transfusion strategy with most advising a hemoglobin threshold of 7 g/dL in asymptomatic patients.[101,103,104,106] The updated American Society of Anesthesiology task force guidelines recommended a restrictive hemoglobin transfusion strategy between 6 g/dL and 10 g/dL that was determined by the potential for ongoing bleeding and other clinical variables.[107] In symptomatic patients, these guidelines suggest that

Table 3. Evidence for the Association Between Red Blood Cell (RBC) Storage Duration and Adverse Patient Outcomes[a]

No. of RCTs	Quality Assessment[b]					Storage Duration of RBCs, No./Total (%)		Effect		Quality of RCTs
	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Fresher[c]	Standard Issue[d]	Relative Risk (95% CI)	Absolute Risk (95% CI)	
Primary Outcome: 30-d Mortality[e]										
13	Not serious	Not serious	Not serious	Serious	None detected	585/2594 (22.6)	597/2921 (20.4)	1.04 (0.95-1.14)	4 more deaths per 1000 (5 fewer deaths to 14 more per 1000)	Moderate
Secondary Outcomes										
Adverse Events										
3	Not serious	Not serious	Serious	Serious	None detected	288/1781 (16.2)	295/1804 (16.4)	1.02 (0.91-1.14)	1 more adverse event per 1000 (2 fewer events to 4 more per 1000)	Low
Nosocomial Infections										
4	Not serious	Not serious	Serious	Serious	None detected	605/1958 (30.9)	568/1982 (28.7)	1.09 (1.00-1.18)	43 more infections per 1000 (1 more infection to 86 more per 1000)	Low

Abbreviation: RCT, randomized clinical trial.

[a] This Table was modified from the meta-analysis published by Alexander et al[44] with the addition of 1 trial.[39] This Table addresses the question of whether fresher blood compared with standard-issue blood should be used for patients of any age treated for a medical emergency or surgery at hospitals, intensive care units, and emergency departments.

[b] Evaluates the risk of bias, inconsistency based on the heterogeneity among trials, indirectness based on the generalizability of the results, imprecision based on the width of the 95% CIs, and publication bias based on some trials not being published. The Grading of Recommendations Assessment, Development and Evaluation method (eAppendix in the Supplement) was used.

[c] Ten studies defined fresher storage duration as 3 days to 10 days; 2 studies defined it as the freshest blood in inventory; and 1 study defined it as less than 20 days.

[d] Nine studies just used the term *standard issue* and storage duration was not provided, 3 studies defined it as greater than or equal to 20 days, and 1 study defined it as 25 days to 35 days.

[e] Based on a composite of the longest follow-up period provided in each trial including 30 days, 90 days, and in-hospital mortality.

transfusion should be administered to prevent symptoms.[102,103,106] The guidelines from the National Blood Authority of Australia emphasized that the hemoglobin level alone should not dictate transfusion but that it should also be based on clinical status.[103] The guidelines from the National Comprehensive Cancer Network for patients with anemia induced by cancer and chemotherapy did not address whether thrombocytopenia should influence transfusion thresholds but suggested transfusion for symptoms.[106]

In contrast to the AABB recommendations, several guidelines provided specific guidance for patients with acute coronary syndrome that differ from guideline to guideline. The British Committee for Standards in Haematology recommended hemoglobin level be maintained at 8 g/dL to 9 g/dL.[104] The National Comprehensive Cancer Network recommended a hemoglobin transfusion goal of greater than 10 g/dL.[106] The National Blood Authority of Australia recommended that a hemoglobin level greater than 8 g/dL be maintained to possibly reduce mortality but that higher levels are uncertain.[103] The European Society of Cardiology recommended transfusion for patients with a hemoglobin level of less than 7 g/dL unless the patient is not hemodynamically stable.[100] The American College of Physicians recommended a hemoglobin transfusion threshold of 7 g/dL to 8 g/dL in hospitalized patients who have either coronary heart disease or acute coronary syndrome.[105]

The AABB recommendation for RBC storage is more specific than those from other groups, which were promulgated prior to publication of most of the RCTs that provided evidence for the AABB recommendation. For example, the British Committee for Standards in Haematology and the American College of Critical Care Medicine noted a lack of evidence to recommend fresher compared with standard issue RBCs.[10,104] The Australian and New Zealand Society of Blood Transfusion suggested that fresher RBCs (<5 days old) may be indicated in special situations for children and neonates.[108] The guidelines from the Kidney Disease Improving Global Outcomes Work Group suggests use of fresher RBCs for patients with end-stage renal disease may maximize posttransfusion survival.[102]

Research Recommendations

Areas of uncertainty for which RCTs are needed include trials in patient populations outside the intensive care unit that include but are not limited to patients with anemia and thrombocytopenia, patients requiring chronic transfusions and those with coagulopathy, hemorrhagic shock, or both. Furthermore, trials that examine lower hemoglobin transfusion thresholds are needed in patients with acute coronary syndrome and those with cardiovascular disease. A recent meta-analysis of selected trials found a higher risk of acute coronary syndrome but not 30-day morality among patients with cardiovascular disease who received a restrictive transfusion strategy compared with a liberal transfusion strategy.[109] Although ongoing trials[110-112] evaluating RBC storage duration should be completed, additional trials do not appear warranted at this time.

Conclusions

Research in RBC transfusion medicine has significantly advanced the science in recent years and provides high-quality evidence to inform guidelines. A restrictive transfusion threshold is safe in most clinical settings and the current blood banking practices of using standard-issue blood should be continued.

ARTICLE INFORMATION

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