JAMA | Special Communication

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.

JAMA. 2016;316(19):2025-2035. doi:10.1001/jama.2016.9185
Published online October 12, 2016.

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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.

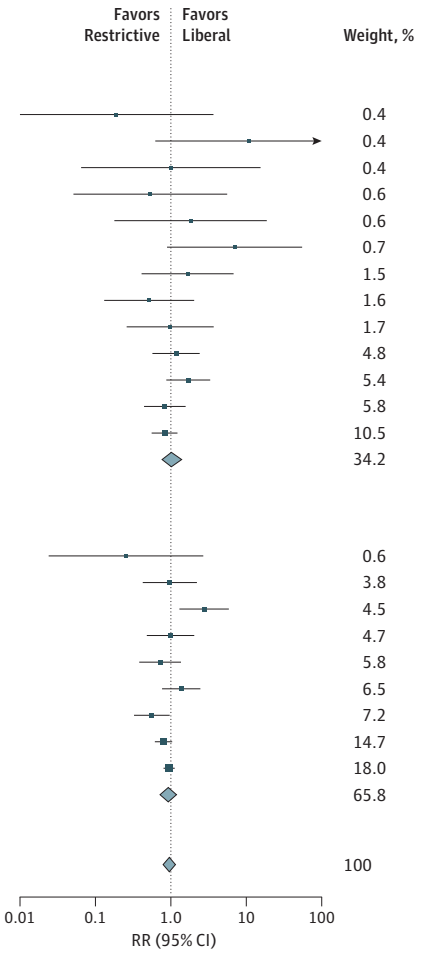
[e] Studies had moderately wide 95% CIs.

[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.

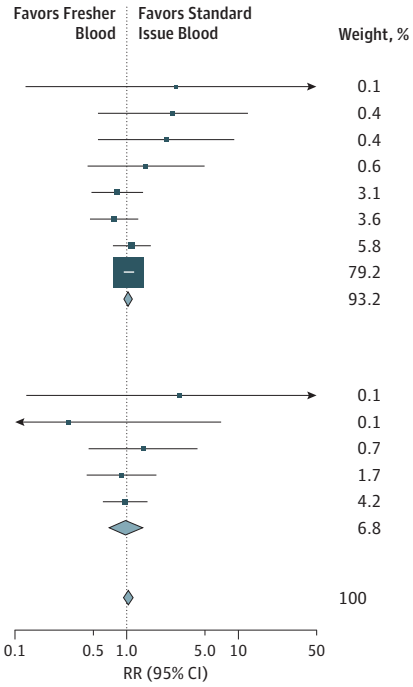
A forest plot shows no evidence that transfusion of fresher RBCs is superior to standard issue RBCs for the outcome of mortality (RR, 1.04; 95% CI, 0.95-1.14) with similar estimates in both adults and infants (**Figure 2**). The association of RBC storage duration on 3 clinical outcomes reported in the 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

Published Online: October 12, 2016. doi:10.1001/jama.2016.9185

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Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Grossman reported receiving research support from Fresenius Kabi. Dr Cohn reported receiving grants and personal fees from Fenwal (a Fresenius Kabi company) and Ortho Clinical Diagnostics; and grants fom Octapharma. Dr Roback reported receiving personal fees from MacoPharm US, Castle Medical Inc, CSL Plasma Inc; personal fees and stock options from Transfusion and Transplantation Technologies Inc and Cambium Medical Technologies; and grants and personal fees from Biomet. Dr Shander reported receiving grants and speaker fees from CSL Behring and Masimo Corporation; speakers fees from Merck; serving as a consultant to AMAG Pharmaceuticals, Gauss Surgical, and Vifor Pharma; and receiving grants and serving as a consultant to HbO_2 Therapeutics LLC. No other disclosures were reported.

Funding/Support: Support for guideline development was provided by the AABB (previously known as the American Association of Blood Banks).

Role of the Funder/Sponsor: The AABB had a role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Additional Contributions: The AABB (previously known as the American Association of Blood Banks) staff member was Theresa Wiegmann, JD, who was not paid outside her usual salary.

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