

JAMA | Special Communication

Red Blood Cell Transfusion

2023 AABB International Guidelines

Jeffrey L. Carson, MD; Simon J. Stanworth, MD, DPhil; Gordon Guyatt, MD; Stacey Valentine, MD, MPH; Jane Dennis, PhD; Sara Bakhtary, MD; Claudia S. Cohn, MD, PhD; Allan Dubon, MLS; Brenda J. Grossman, MD, MPH; Gaurav K. Gupta, MD, PhD; Aaron S. Hess, MD, PhD; Jessica L. Jacobson, MD; Lewis J. Kaplan, MD; Yulia Lin, MD; Ryan A. Metcalf, MD; Colin H. Murphy, MD; Katerina Pavenski, MD; Micah T. Prochaska, MD; Jay S. Raval, MD; Eric Salazar, MD, PhD; Nabihah H. Saifee, MD, PhD; Aaron A. R. Tobian, MD, PhD; Cynthia So-Osman, MD, PhD; Jonathan Waters, MD; Erica M. Wood, MD; Nicole D. Zantek, MD, PhD; Monica B. Pagano, MD

IMPORTANCE Red blood cell transfusion is a common medical intervention with benefits and harms.

OBJECTIVE To provide recommendations for use of red blood cell transfusion in adults and children.

EVIDENCE REVIEW Standards for trustworthy guidelines were followed, including using Grading of Recommendations Assessment, Development and Evaluation methods, managing conflicts of interest, and making values and preferences explicit. Evidence from systematic reviews of randomized controlled trials was reviewed.

FINDINGS For adults, 45 randomized controlled trials with 20 599 participants compared restrictive hemoglobin-based transfusion thresholds, typically 7 to 8 g/dL, with liberal transfusion thresholds of 9 to 10 g/dL. For pediatric patients, 7 randomized controlled trials with 2730 participants compared a variety of restrictive and liberal transfusion thresholds. For most patient populations, results provided moderate quality evidence that restrictive transfusion thresholds did not adversely affect patient-important outcomes. Recommendation 1: for hospitalized adult patients who are hemodynamically stable, the international panel recommends a restrictive transfusion strategy considering transfusion when the hemoglobin concentration is less than 7 g/dL (strong recommendation, moderate certainty evidence). In accordance with the restrictive strategy threshold used in most trials, clinicians may choose a threshold of 7.5 g/dL for patients undergoing cardiac surgery and 8 g/dL for those undergoing orthopedic surgery or those with preexisting cardiovascular disease. Recommendation 2: for hospitalized adult patients with hematologic and oncologic disorders, the panel suggests a restrictive transfusion strategy considering transfusion when the hemoglobin concentration is less than 7 g/dL (conditional recommendations, low certainty evidence). Recommendation 3: for critically ill children and those at risk of critical illness who are hemodynamically stable and without a hemoglobinopathy, cyanotic cardiac condition, or severe hypoxemia, the international panel recommends a restrictive transfusion strategy considering transfusion when the hemoglobin concentration is less than 7 g/dL (strong recommendation, moderate certainty evidence). Recommendation 4: for hemodynamically stable children with congenital heart disease, the international panel suggests a transfusion threshold that is based on the cardiac abnormality and stage of surgical repair: 7 g/dL (biventricular repair), 9 g/dL (single-ventricle palliation), or 7 to 9 g/dL (uncorrected congenital heart disease) (conditional recommendation, low certainty evidence).

CONCLUSIONS AND RELEVANCE It is good practice to consider overall clinical context and alternative therapies to transfusion when making transfusion decisions about an individual patient.

JAMA. doi:10.1001/jama.2023.12914
Published online October 12, 2023.

- [+ Viewpoint](#)
- [+ Supplemental content](#)
- [+ CME at \[jamacmelookup.com\]\(https://jamacmelookup.com\)](#)

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Jeffrey L. Carson, MD, Department of Medicine, Rutgers Robert Wood Johnson Medical School, 125 Paterson St, New Brunswick, NJ 08901 (jeffrey.carson@rutgers.edu).

Red blood cell (RBC) transfusion is a common and costly treatment; approximately 118 million units of blood are collected worldwide each year.^{1,2} Clinicians should offer RBC transfusion to patients only when benefits outweigh harms. Harms include infectious and noninfectious complications; although serious reactions are infrequent, there remains potential for substantial harm (Table 1).^{3,4} Patient advocacy groups support minimizing harms by avoiding transfusions without clear benefit.⁵

Although the average acquisition cost of a unit of RBCs is \$215 in the United States,^{6,7} it varies by country and region. Acquisition costs do not typically cover expenses of distribution, storage, processing, administration, and monitoring for complications.^{7,8} Many blood transfusion providers face challenges, exacerbated by the COVID-19 pandemic, in maintaining adequate stocks of RBCs.⁹

Randomized controlled trials (RCTs) assessing outcomes of different transfusion thresholds typically compare higher hemoglobin thresholds (liberal transfusion strategy) with lower ones (restrictive transfusion strategy) for RBC transfusions. The numbers of these trials continue to increase. AABB guidelines in 2012 included 19 RCTs; in 2016, 31 RCTs.^{10,11} In 2018, the Transfusion and Anemia Expertise Initiative published guidelines based on 5 RCTs for RBC transfusion in critically ill children.¹² In 2021, an updated Cochrane systematic review included 48 trials.¹³ Given the expanded evidence base and the prior absence of AABB guidelines specific to children, we reexamined the transfusion threshold evidence and provide updated guidance.

Guideline Development Process

The AABB commissioned and funded updated guidelines through the AABB Clinical Transfusion Medicine Committee. To encourage wide implementation of the recommendations, the board of directors supported recruiting experts in RBC transfusion from international professional organizations (eAppendix in the Supplement). These recommendations were developed in collaboration with and are endorsed by the International Society of Blood Transfusion, International Collaboration for Transfusion Medicine Guidelines, the Society of Critical Care Medicine, the European Blood Alliance, and the Society for the Advancement of Patient Blood Management.

These guidelines follow existing standards of trustworthiness,¹⁴ including use of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach for summarizing evidence and moving from evidence to recommendations¹⁵ to provide credible recommendations for clinicians caring for adults and children considered for RBC transfusions. These guidelines do not address transfusion in preterm neonates.

Perspective

The panel chose individual patients as the primary perspective but also considered public health considerations; for example, supply of blood.

Panel Composition and Conflicts

The international panel included members with expertise in transfusion medicine, supported by a GRADE methodologist (G.G.) and a patient partner (A.D.) (eAppendix in the Supplement). In accordance with

Table 1. Approximate Per-Unit Risk for Red Blood Cell (RBC) Transfusion in the US^a

Adverse event	Approximate risk per RBC transfusion
Febrile reaction	1:161 ³
Allergic reaction	1:345 ³
Transfusion-associated circulatory overload	1:125 ³
Transfusion-related acute lung injury	1:1250 ³
Anaphylactic reactions	1:5000 ³
Hepatitis B virus	1:1 100 000 ⁴
Hepatitis C virus	1:1 200 000 ⁴
HIV	1:1 600 000 ⁴

^a The incidence of noninfectious complications of transfusion reactions is based on active surveillance from 4 institutions. These rates will vary according to patient population (national databases vs hospital experience) and reporting practices and criteria (active, passive, severity, case definition, and others). The estimated incidence of infectious complications is derived from the Transfusion-Transmissible Infections Monitoring System.

AABB policy, individual members disclosed all potential financial, professional, or personal conflicts of interest; none had substantive conflicts.¹⁶ Five members were authors of trials included in a systematic review on transfusion thresholds (J.L.C., S.J.S., Y.L., C.S.-O., and E.M.W.) and did not vote on corresponding recommendations.

Population, Intervention, Comparator, and Outcomes Questions

We provide recommendations for 2 questions:

1. For hospitalized, hemodynamically stable adult patients, should clinicians transfuse with a restrictive strategy (typical hemoglobin level <7-8 g/dL) vs a liberal strategy (typical hemoglobin level <9-10 g/dL)?
2. For hospitalized, hemodynamically stable pediatric patients (a) without congenital heart disease (infancy to 16 years), should clinicians transfuse with a restrictive strategy (hemoglobin level <7-8 g/dL) vs a liberal strategy (hemoglobin level <9-10 g/dL); and (b) with congenital heart disease, should clinicians transfuse with a restrictive vs liberal strategy based on the cardiac lesion?

We provide recommendations for patients with acute or prolonged need of transfusions, but not for those who are transfusion dependent (eg, hemoglobinopathies). For adults, we examined subgroups in which the harm and benefit of a particular transfusion threshold might differ from that of overall populations: preexisting coronary artery disease, cardiac surgery, orthopedic surgery, and oncologic or hematologic conditions.

We examined subgroups of children in whom the risk and benefit of transfusion threshold might differ from that of the overall populations of patients: those with heart disease (congenital or acquired) or surgery and hematologic or oncologic conditions. We excluded trials of preterm neonates, which have been reviewed elsewhere.¹⁷

Values and Preferences

Recommendations are based on the following values and preferences:

- Avoid the adverse effects after RBC transfusion (high value).
- Conserve resources related to RBC transfusions (high value) to ensure blood is available for individuals who need it most.
- Prefer the demonstrated benefits of a restrictive transfusion policy despite the remaining possibility of a small increase in mortality.

Comments and Modification

J.L.C., S.J.S., G.G., S.V., and M.B.P. prepared the draft guideline document that was modified and approved by all panel members and the AABB Clinical Transfusion Medicine Committee. Subsequently, the AABB board of directors and international partner organizations also reviewed the guidelines.

Evidence Review and Grading

Systematic Review

We developed recommendations based on recently published systematic reviews of transfusion thresholds in adults (Cochrane review conducted in 2021)¹³ and children (Transfusion and Anemia Expertise Initiative, 2018),¹² supported by literature searches up to February 2021. We reviewed evidence from 45 RCTs with 20 599 adults, 5 RCTs identified within the Transfusion and Anemia Expertise Initiative in 2018, and 2 additional pediatric trials (the 5 RCTs and 2 pediatric trials had a total of 2730 participants).¹⁸⁻²⁰ The systematic reviews included RCTs in which the transfusion groups were assigned based on a clear transfusion threshold, described as the hemoglobin concentration or hematocrit level required before RBC transfusion. Outcomes in adults included 30-day mortality, nonfatal myocardial infarction, pulmonary edema or congestive heart failure, stroke, thromboembolism, acute kidney injury, infection, hemorrhage, mental confusion, proportion of patients with an allogeneic or autologous RBC transfusion, hemoglobin concentration (postoperative or discharge), number of RBC units transfused, and quality of life. An updated search conducted in January 2023 identified 3 trials with 151 patients.²¹⁻²³ For children, outcomes included mortality, thromboembolism, infection, and transfusion requirements.

Analysis

We assessed risk of bias in each RCT as recommended by Cochrane,²⁴ assessed statistical heterogeneity by both I^2 and χ^2 tests,²⁵ and used the Instrument to Assess the Credibility of Effect Modification Analyses criteria for making inferences regarding subgroup effects.²⁶ All analyses were performed with Review Manager version 5.4 (Cochrane Collaboration).²⁷ Relative risks and the corresponding 95% CIs were calculated for each outcome with random-effects models²⁸ unless counterintuitive results mandated use of a fixed-effect model. We calculated absolute risks by applying the relative effect to the median of control group risks. When events were anticipated to be rare (eg, for thromboembolism), the Peto odds ratio informed relative effect estimates.

Rating Quality of Evidence and Making Recommendations

We used GRADE methodology to develop these guidelines (see the [Supplement](#)).^{15,29} The panel came to consensus for quality of evidence ratings that were included in summary of findings tables that served as the bases for panel judgments.³⁰ In moving from evidence to recommendations, the panel considered criteria in GRADE's evidence to decision framework.³¹ The panel came to consensus for all recommendations except for using different restrictive strategy thresholds by clinical subgroup in which a vote was required.

Good Practice Statement

In deciding when a particular patient should undergo transfusion, the panel considers it good clinical practice to consider not only the hemoglobin concentration but also symptoms, signs, other laboratory data, patients' values and preferences, and the overall clinical context. Relevant variables include the rate of hemoglobin level decline, intravascular volume status, dyspnea, decreased exercise tolerance, lightheadedness, chest pain thought to be cardiac in origin, and hypotension or tachycardia unresponsive to fluid challenge. Clinicians should consider alternatives to transfusion, including medical treatment of anemia and blood conservation strategies.

Disclaimer

This practice guideline will not apply to all individual RBC transfusion decisions.

Recommendations for Adults

Recommendation 1

For hospitalized adult patients who are hemodynamically stable, the international panel recommends a restrictive RBC transfusion strategy in which the transfusion is considered when the hemoglobin concentration is less than 7 g/dL (strong recommendation, moderate certainty evidence).

Remark: in accordance with the restrictive strategy threshold used in most of the trials for subgroups of patients, clinicians may choose a threshold of 7.5 g/dL for patients undergoing cardiac surgery and 8 g/dL for patients undergoing orthopedic surgery or those with preexisting cardiovascular disease.

Recommendation 2

For hospitalized adult patients, the panel suggests a restrictive RBC transfusion strategy in which transfusion is considered when the hemoglobin concentration is less than 7 g/dL in those with hematologic and oncologic disorders (conditional recommendation, low certainty evidence).

Evidence Summary for Adults

The 45 RCTs with adult participants were conducted across a range of settings, including orthopedic surgery (n = 11), cardiac surgery (n = 8), hematologic and oncologic conditions (n = 7), critical care (n = 8), acute blood loss (n = 6), acute myocardial infarction (n = 3), and vascular surgery (n = 2). The most common liberal transfusion threshold was 9 to 10 g/dL and the most common restrictive threshold was 7 to 8 g/dL.

Table 2 presents the summary of findings comparing restrictive with liberal transfusion strategies for 30-day mortality, multiple morbidities, and transfusion requirements. Thirty trials including data from 16 092 participants evaluated 30-day mortality, with a pooled relative risk of 1.00 (95% CI, 0.86-1.16). The baseline mortality rate was 8.3%, and an absolute difference between transfusion strategies was 0% (95% CI, 1.2% fewer to 1.3% more deaths) (high certainty). The restrictive strategy resulted in a 32.4% absolute reduction (95% CI, 37.3%-27.5% fewer deaths) in receiving a transfusion.

Chance may explain differences in mortality estimates among the clinical conditions (test for subgroup differences, $P = .34$). Given limited trial data in hematologic malignancies (2 trials, N = 149 participants) and an upper CI limit consistent with substantial harm

Table 2. Summary of Findings in Trials Comparing Liberal vs Restrictive Transfusion Strategies on Mortality, Morbidity, and Blood Transfusion in Adults

Outcome, No. of participants (No. of RCTs)	Relative effect (95% CI)	Absolute effects, %			Certainty	Plain language summary
		Restrictive	Liberal	Difference (95% CI)		
30-d Mortality, N = 16 092 (30)	RR, 1.00 (0.86-1.16)	8.3	8.3	0.0 Fewer (1.2 fewer to 1.3 more)	High	Transfusion threshold likely has little or no effect on mortality
MI, N = 14 370 (23)	RR, 1.04 (0.87-1.24)	3.3	3.2	0.1 More (0.4 fewer to 0.8 more)	High	Transfusion threshold has little or no effect on MI
CHF, N = 6610 (15)	RR, 0.86 (0.56-1.33)	3.2	3.7	0.5 Fewer (1.6 fewer to 1.2 more)	Low ^{a,b}	Transfusion threshold likely has little or no effect on CHF
CVA, N = 13 985 (19)	RR, 0.84 (0.64-1.09)	1.4	1.7	0.3 Fewer (0.6 fewer to 0.2 more)	High	Transfusion threshold likely has little or no effect on CVA
Rebleeding, N = 3412 (8)	RR, 0.80 (0.59-1.09)	12.6	15.8	3.2 Fewer (6.5 fewer to 1.4 to more)	Moderate ^a	Transfusion threshold likely has little or no effect on rebleeding
Infection, N = 16 466 (24)	RR, 0.98 (0.89-1.09)	13.6	13.9	0.3 Fewer (1.5 fewer to 1.2 more)	High	Transfusion threshold likely has little or no effect on infection
Thromboembolism, N = 4201 (13)	OR, 1.11 (0.65-1.88)	1.7	1.5	0.2 More (0.5 fewer to 1.3 more)	Moderate ^b	Transfusion threshold likely has little or no effect on thromboembolism
Delirium, N = 6442 (9)	RR, 1.11 (0.88-1.40)	11.9	10.7	1.2 More (1.3 fewer to 4.3 more)	Moderate ^b	Transfusion threshold likely has little or no effect on delirium
Transfusion, N = 19 419 (41)	RR, 0.60 (0.54-0.66)	48.6	81.0	32.4 Fewer (37.3 to 27.5 fewer)	High	Restrictive transfusion threshold results in large reduction in transfusion

Abbreviations: CHF, congestive heart failure; CVA, cerebrovascular accident; MI, myocardial infarction; OR, odds ratio; RCT, randomized controlled trial; RR, relative risk.

^b Downgraded for imprecision. 95% CIs were calculated with Review Manager version 5.4 (Cochrane).²⁷ See eFigures 1 through 9 in the Supplement for details.

^a Downgraded for inconsistency.

Table 3. Summary of Findings in Trials of Patients With Hematologic Malignancies and Myocardial Infarction Comparing Liberal vs Restrictive Transfusion Strategies on 30-Day Mortality

Patient group (No. of RCTs)	30-d Mortality relative effect (95% CI)	Absolute effects, %			Certainty
		Restrictive	Liberal	Difference (95% CI)	
Hematologic malignancies, N = 149 (2)	RR, 0.37 (0.07-1.95)	2.4	6.6	4.1 fewer (6.1 fewer to 6.2 more)	Low ^a
Myocardial infarction, N = 820 (3)	RR, 0.99 (0.59-1.65) ^b	6.7	6.8	0.1 fewer (2.8 fewer to 4.4 more)	Low ^{c,d}

Abbreviations: RCT, randomized controlled trial; RR, relative risk.

absolute difference = 4.1% more (4.2 fewer and 39.7 more).

^a Two downgrades for very serious imprecision.

^c Imprecision.

^b Note that in consultation with a methodologist (GG), a fixed effect model has been presented for this outcome due to low event rate. Random effects model

^d Inconsistency. 95% CIs calculated with Review Manager version 5.4 (Cochrane Collaboration).²⁷

(6.2% rate of increased deaths in the restrictive transfusion strategy), certainty of the evidence for mortality in this population was rated low (Table 3). Given heterogeneity in results and an upper CI limit consistent with substantial harm (4.4% rate of increased deaths in the restrictive transfusion strategy), the certainty of the evidence was rated low for mortality in acute myocardial infarction (Table 3).

There were no apparent differences between transfusion strategies for the morbidity outcomes (Table 2). Data from 3 RCTs that enrolled 448 participants suggested the risk of bleeding in hematology and oncology patients was uninfluenced by transfusion strategy (relative risk, 1.03; 95% CI, 0.87 to 1.23; absolute difference, 0.6%; 2.7% fewer to 4.8% more bleeding events).³²⁻³⁴

The most common restrictive transfusion strategy applied in the trials was 7 or 8 g/dL (Figure), although variations included critical care and cardiac surgery trials that used a transfusion strategy of 7 to 7.5 g/dL and orthopedic and acute myocardial infarction trials that used a restrictive strategy of 8 g/dL.³⁶⁻⁶⁴

Rationale for Recommendations for Adults

The panel recommends that RBC transfusion be administered using a restrictive transfusion strategy of 7 g/dL for most hemody-

namically stable adults (strong recommendation, high certainty evidence).

The panel was divided (by vote) on whether to recommend different restrictive transfusion strategy thresholds by clinical subgroup. The rationale for recommending a universal threshold of 7 g/dL is that many trials used this threshold, and there is no strong clinical or biological basis for expecting different effects between 7 and 8 g/dL (with the possible exception of cardiovascular disease and hematology or oncology; see later). Furthermore, the effects on mortality were consistent across all subgroups, and there were no apparent differences in outcomes between trials that used a threshold of 7 and 8 g/dL (see earlier) (Figure). Recommending a hemoglobin threshold of 7 g/dL would conserve more blood.

An alternative view is that the recommendations should closely follow the clinical trial evidence and avoid extrapolating trial results when a threshold of 7 g/dL has not been explicitly tested. Most of the trials in orthopedic surgery used a threshold of 8 g/dL, and the largest trial conducted in cardiac surgery used a threshold of 7.5 g/dL. Some members of the panel thought that higher hemoglobin thresholds might improve outcomes other than mortality, including improved function and recovery after surgery or acute illness.

Figure. Comparison of Randomized Trials in Adults Using Different Restrictive Transfusions for the Outcome of Mortality at 30 Days

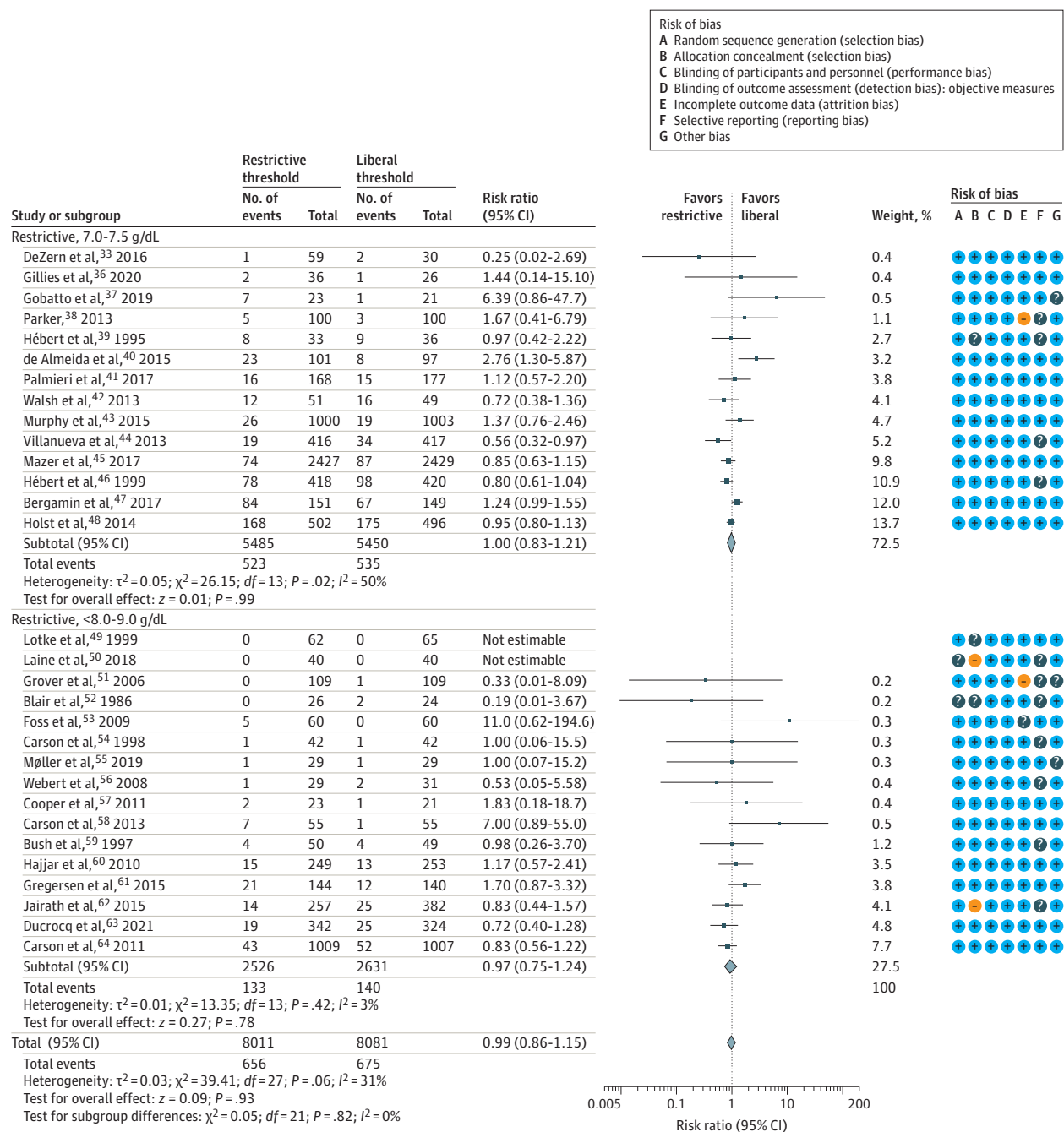


Figure modified from the Cochrane review¹³ by removing 1 trial performed with pediatric patients (Lacroix et al³⁵) and placing a second trial (Laine et al³⁶) in the correct subgroup. Relative risks and the corresponding 95% CIs were calculated

for each outcome with random-effects models unless counterintuitive results mandated use of a fixed-effect model. The blue pluses indicate low risk of bias; gray question marks, unclear risk of bias; and orange minuses, high risk of bias.

For patients with acute and chronic ischemic cardiac disease, there remains substantial uncertainty regarding the safety of restrictive thresholds. As in the AABB's previous guidelines,^{10,11} the panel chose not to recommend for or against a liberal or restrictive transfusion threshold for patients with acute myocardial infarction. Although the pooled estimates of effects on mortality with acute myocardial infarction were almost identical to the overall effects, the

absolute and relative risk estimates were imprecise, with wide CIs. The panel noted that the MINT trial (including 3500 participants with acute myocardial infarction) is nearing completion. MINT compares a liberal transfusion at 10 g/dL with a restrictive transfusion strategy of 7 to 8 g/dL.⁶⁵

In the setting of hematology and oncology inpatients, the panel suggests transfusion at 7 g/dL (conditional, low certainty evidence).

Table 4. Summary of Findings in Trials Comparing Liberal vs Restrictive Transfusion Strategies on Mortality, Morbidity, and Blood Transfusion in Children

Outcome, No. of participants (No. of RCTs)	Relative effect (95% CI)	Anticipated absolute effects (95% CI), %			Certainty	Plain language summary
		Restrictive	Liberal	Difference (95% CI)		
Participants exposed to blood transfusion, 799 (2)	RR, 0.51 (0.41-0.65)	48.0	94.2	46.2 Fewer (55.6 to 33 fewer)	High	Restrictive transfusion threshold has a large effect on reduction of transfusion
30-d Mortality (follow-up range, 28-30 d), 972 (5)	RR, 0.44 (0.04-4.45)	1.7	3.9	2.2 Fewer (3.8 fewer to 13.5 more)	Moderate ^{a,b}	Transfusion threshold likely has little effect on mortality
Pneumonia, 744 (2)	RR, 1.14 (0.58-2.23)	4.6	4.0	0.6 More (1.7 fewer to 5 more)	Moderate ^a	Transfusion threshold likely has little or no effect on pneumonia
Thrombosis (follow-up, 28 d), 799 (2)	OR, 1.78 (0.61-5.22)	2.3	1.3	1.0 More (0.5 fewer to 5.4 more)	Low ^c	Transfusion threshold may have little or no effect on thrombosis
30-d Mortality subgroup analysis by clinical specialties (cardiac surgery), 454 (4)	RR, 0.62 (0.12-3.13)	1.1	1.8	0.7 Fewer (1.6 to 3.8 more)	Low ^{a,b,d}	Transfusion threshold may have little effect on mortality

Abbreviations: OR, odds ratio; RCT, randomized controlled trial; RR, relative risk.

^a One downgrade for imprecision; even the largest included study was not adequately powered for the outcome of mortality. Smaller studies were not always informative because they included low-risk populations only, terminated early, or reported no or few events.

^b For 1 study reporting mortality data only within the scope of its study period, we obtained supplementary data for 30 days.

^c Two downgrades for serious imprecision (rare event).

^d Downgraded for imprecision. 95% CIs were calculated with Review Manager version 5.4 (Cochrane Collaboration).²⁷ See eFigures 10 through 14 in the Supplement for details.

Although the number of patients enrolled in these trials was smaller than that in many other clinical subgroups, because new RCTs have suggested neither harm nor increased bleeding when using a restrictive threshold, this recommendation differs from the 2016 guidelines.¹¹ There were insufficient trial data to inform recommendations in outpatient transfusion management.

Recommendations for Children

Recommendation 3

For critically ill children and hospitalized children at risk of critical illness who are hemodynamically stable and without a transfusion-dependent hemoglobinopathy, cyanotic cardiac condition, or severe hypoxemia, the international panel recommends a restrictive transfusion strategy in which a transfusion is considered when the hemoglobin level is less than 7 g/dL compared with one of less than 9.5 g/dL (strong recommendation, moderate certainty evidence).

Recommendation 4

The international panel suggests considering a transfusion threshold for hemodynamically stable children with congenital heart disease that is based on the cardiac abnormality and stage of surgical repair: 7 g/dL (biventricular repair), 9 g/dL (single-ventricle palliation), or 7 to 9 g/dL (uncorrected congenital heart disease) (conditional recommendation, low certainty evidence).

Evidence Summary for Children

The populations of children included in the RCTs were critically ill patients ($n = 2$),^{20,35} those with hematologic conditions ($n = 1$),⁶⁶ those with acquired and congenital heart disease ($n = 3$),⁶⁷⁻⁶⁹ and those with severe (malarial) anemia ($n = 1$)^{18,19} (Table 4). The largest single intensive care unit RCT reported a 51.8% absolute reduction in transfusions in the restrictive strategy group compared with the liberal strategy group,³⁵ with no significant difference reported for 30-day mortality within a meta-analysis of 5 RCTs (relative risk, 0.44; 95% CI, 0.04-4.45). In the latter analysis, the baseline mortality rate was 3.9%, with an absolute difference of 1.7% (95% CI,

0.2% fewer to 17.5% more deaths) (moderate certainty). There were no clear differences in the morbidity outcomes (Table 4). We evaluated the transfusion strategies on 30-day mortality in subgroups of heart disease (acquired and congenital) (eFigure 12 in the Supplement). Chance may explain differences in mortality among the clinical populations. The certainty of the evidence was rated as low because of small sample size and various surgical settings and clinical conditions.

Rationale for Recommendations for Children

It is likely that mortality is similar for restrictive strategies compared with liberal ones (moderate certainty, rated down because of inconsistency and the remaining possibility of an increase in 30-day mortality after application of a restrictive strategy of up to 3%).

Although the direct evidence was dominated by a single trial,³⁵ a large well-conducted RCT of transfusion volumes and timing in anemic children (hemoglobin level <6 g/dL) with malaria also supported the safety of a restrictive transfusion threshold. The panel concluded this evidence supported a strong recommendation.^{18,19}

Children with acquired or congenital heart disease form a subgroup in which there remains uncertainty regarding the pathophysiologic safety of restrictive thresholds, and the RCTs had recruited different populations of children undergoing surgery.

Discussion

The expanding number of RCTs of RBC transfusion thresholds informs best practice in adults and children. Many of the RCTs tested different protocols including thresholds for RBC transfusion that varied by clinical setting. The panel debated whether to recommend a threshold of 7 g/dL for all hemodynamically stable adults or adopt a higher threshold in select clinical subgroups (cardiac surgery, 7.5 g/dL; orthopedic surgery and chronic cardiovascular disease, 8 g/dL), ultimately concluding that each approach has its merits. Our guideline also now incorporates specific guidance

for hemodynamically stable children, and the findings support recommendations for a restrictive strategy (threshold <7 g/dL for children, excluding those with congenital heart disease). Minimizing unnecessary complications of transfusion and responding to the ongoing global challenges of having a safe and secure blood supply will require effective strategies, including blood management programs, for implementation of these guidelines.

Good transfusion practice should rely not only on hemoglobin concentration thresholds but also incorporation of patients' symptoms, signs, comorbid conditions, rate of bleeding, values, and preferences. This guidance is particularly important because clinicians commonly use only hemoglobin concentration to decide when to transfuse.⁷⁰ Blood management programs that audit blood should attend to these broader considerations in their policies and decisions. Given that RCTs demonstrated no effect on mortality,^{71,72} the storage age of transfused RBCs need not be considered in transfusion decisions.

Similar to older guidelines,⁷³⁻⁷⁸ this guideline and other guidelines published after 2016 continue to recommend restrictive transfusion strategies⁷⁹⁻⁸³ (Box).

Research Recommendations

Ongoing trials for patients with acute myocardial infarction, vascular disease, and neurologic disorders will inform transfusion practice.¹⁷ Further analyses of subgroups of trials using individual patient data from existing trials are needed by age, sex, preexisting cardiovascular disease, pregnancy status, and other clinical factors. There are gaps in the evidence regarding the needs of individuals with myelodysplastic syndromes who are transfusion dependent. To modify symptoms of anemia, such people may require higher thresholds for transfusions. Given the findings indicating the safety of restrictive thresholds, new trial designs should focus on the safety of lower transfusion thresholds (eg, 5-6 g/dL), incorporation of physiologic parameters, and the conduct of health economic analyses.

Conclusion

Our panel recommends restrictive transfusion strategies, typically with a threshold of 7 g/dL for both adult and pediatric patients. The

Box. Red Blood Cell Transfusion Guidelines Since 2016

Society and Recommendation

UK National Clinical Guidelines Centre (2016)⁷⁹

Restrictive threshold (7 g/dL) for patients who do not have major hemorrhage or acute coronary syndrome or need long-term transfusion. In acute coronary syndrome, transfusion should be considered at a threshold of 8 g/dL. Clinicians should consider setting individual targets for patients with chronic anemia.

European Society of Anaesthesiology (2017)⁸⁰

Target hemoglobin level of 7-9 g/dL in patients with active bleeding

Frankfurt Germany Consensus conference (2018)⁸¹

Varied depending on clinical setting: 7 g/dL for critically ill patients, 7.5 g/dL in cardiac surgery, 8 g/dL in hip fracture and cardiovascular disease, and 7-8 g/dL in acute gastrointestinal bleeding

Pediatric Critical Care Transfusion and Anemia Expertise Initiative (2018)¹²

Varied depending on clinical setting: 7 g/dL for hemodynamically stable critically ill children; for hemodynamically stable children with congenital heart disease, varied based on cardiac abnormality and stage of repair; 7 g/dL biventricular repair, 9 g/dL stage 1 and stage 2 palliation

Society of Cardiovascular Anesthesiologists (2019)⁸²

Transfusion threshold of 7.5 g/dL is reasonable in cardiac surgery

The Society of Thoracic Surgeons and affiliated groups (2021)⁸³

Restrictive transfusion strategy, although a specific hemoglobin level was not provided

panel recognizes important additional considerations, including signs, symptoms, comorbid conditions, and patient values and preferences, that will differ between patients. The recommendation is strong, based on moderate certainty evidence for most patients, but conditional, based on lower certainty evidence subgroups that include hematologic and oncologic disorders in adults and cyanotic cardiac condition in infants.

ARTICLE INFORMATION

Accepted for Publication: June 26, 2023.

Published Online: October 12, 2023.
doi:10.1001/jama.2023.12914

Author Affiliations: Department of Medicine, Rutgers Robert Wood Johnson Medical School, New Brunswick, New Jersey (Carson); Department of Haematology, Oxford University Hospitals NHS Trust, Oxford, United Kingdom (Stanworth); NHSBT, Oxford, United Kingdom (Stanworth); Radcliffe Department of Medicine, University of Oxford, Oxford, United Kingdom (Stanworth); Department of Transfusion Medicine, NHS Blood and Transplant, Oxford, United Kingdom (Stanworth); Departments of Clinical Epidemiology and Biostatistics and Medicine, McMaster University, Hamilton, Ontario, Canada (Guyatt); Department of Pediatrics, University of Massachusetts Chan Medical School, Worcester (Valentine); Cochrane Injuries Group, London

School of Hygiene and Tropical Medicine, London, United Kingdom (Dennis); Department of Laboratory Medicine, University of California, San Francisco (Bakhtary); Department of Laboratory Medicine and Pathology, University of Minnesota, Minneapolis (Cohn); Patient partner (Dubon); Department of Pathology and Immunology, Washington University School of Medicine in St Louis, St Louis, Missouri (Grossman); Department of Pathology and Laboratory Medicine, Memorial Sloan Kettering Cancer Center, New York, New York (Gupta); Departments of Anesthesiology and Pathology and Laboratory Medicine, University of Wisconsin–Madison, Madison (Hess); Department of Pathology, New York University Grossman School of Medicine, New York (Jacobson); NYC Health + Hospitals/Bellevue, New York, New York (Jacobson); Department of Surgery, Division of Trauma, Surgical Critical Care and Surgical Emergencies, Perelman School of Medicine, University of Pennsylvania, Philadelphia

(Kaplan); Precision Diagnostics and Therapeutics Program, Sunnybrook Health Sciences Centre, Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, Ontario, Canada (Lin); Department of Pathology, University of Utah, Salt Lake City (Metcalfe); Pathology Associates of Albuquerque, Albuquerque, New Mexico (Murphy); Department of Laboratory Medicine and Pathobiology, University of Toronto and St Michael's Hospital–Unity Health Toronto, Toronto, Ontario, Canada (Pavenski); Department of Medicine, University of Chicago, Chicago, Illinois (Prochaska); Department of Pathology, University of New Mexico, Albuquerque (Raval); Department of Pathology and Laboratory Medicine, UT Health San Antonio, San Antonio, Texas (Salazar); Department of Laboratory Medicine and Pathology, Seattle Children's Hospital, Seattle, Washington (Saifee); Department of Pathology, Johns Hopkins University, Baltimore, Maryland (Tobian);

Department of Unit Transfusion Medicine (UTG), Sanquin Blood Bank, Amsterdam, the Netherlands (So-Osman); Department Hematology, Erasmus Medical Center, Rotterdam, the Netherlands (So-Osman); Department of Anesthesiology and Perioperative Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania (Waters); Department of Haematology, Monash Health, Monash University School of Public Health and Preventive Medicine, Melbourne, Victoria, Australia (Wood); Department of Laboratory Medicine and Pathology, University of Minnesota, Minneapolis (Zantek); Department of Laboratory Medicine and Pathology, University of Washington, Seattle (Pagano).

Author Contributions: Drs Carson and Stanworth had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Carson, Stanworth, Guyatt, Valentine, Bakhtary, Cohn, Grossman, Kaplan, Prochaska, Wood, Pagano.

Acquisition, analysis, or interpretation of data: Carson, Stanworth, Guyatt, Dennis, Bakhtary, Cohn, Dubon, Grossman, Gupta, Hess, Jacobson, Kaplan, Lin, Metcalf, Murphy, Pavenski, Prochaska, Raval, Salazar, Saifee, Tobian, So-Osman, Waters, Zantek, Pagano.

Drafting of the manuscript: Carson, Stanworth, Valentine, Dennis, Kaplan, Murphy, Prochaska, Waters, Pagano.

Critical review of the manuscript for important intellectual content: Dennis, Dubon, Hess, Metcalf, Pavenski, Raval, Salazar, Zantek.

Statistical analysis: Carson, Stanworth, Dennis, Hess, Pagano.

Obtained funding: Cohn.

Administrative, technical, or material support: Carson, Valentine, Dennis, Cohn, Hess, Salazar, Tobian, Wood, Pagano.

Supervision: Carson, Stanworth, Guyatt, Cohn, Prochaska, Raval, Waters, Pagano.

Patient perspective: Dubon.

Served as guideline development panelist: Pavenski. **Representative of the International Society of Blood Transfusion:** Wood.

Clinical content expert and European representative: So-Osman.

Other: Kaplan, Prochaska.

Part of the committee involved in the guidelines drafting, review, and discussion: Salazar.

Conflict of Interest Disclosures: Dr Carson reported serving as chair of the data and safety monitoring board for Cerrus for a clinical trial on a treatment system to pathogen-reduce human blood products outside the submitted work; being the principal investigator of a National Heart, Lung, and Blood Institute–supported trial called Myocardial Ischemia and Transfusion, which is evaluating transfusion thresholds in patients with acute myocardial infarction; and receiving financial support paid to his institution. Dr Stanworth reported receiving grants from multiple clinical trials of red blood cell transfusion to his institution, but no direct financial benefits outside the submitted work; receiving grants for red blood cell transfusion trials through his institutions; and being employed by NHSBT, who processes and manufactures red blood cells for transfusion in England. Dr Cohn reported being a paid staff member (chief medical officer) of the AABB during the conduct of the study. Dr Kaplan reported receiving a stipend from the Society of Critical Care Medicine for serving as president from 2020 to 2021 outside the submitted

work. Dr Lin reported receiving grants from Canadian Blood Services, consulting for Choosing Wisely Canada, and receiving grants from Octapharma outside the submitted work. Dr Metcalf reported receiving speakers honoraria from Cerus Corporation outside the submitted work. Dr Pavenski reported serving as vice chair of the International Collaboration for Transfusion Medicine Guidelines and as director for North America, as well as serving on the board of directors for the International Society of Blood Transfusion. Dr Prochaska reported receiving fees for medicolegal consulting outside the submitted work. Dr Raval reported receiving consultancy fees from Sanofi Genzyme outside the submitted work. Dr Saifee reported nonfinancial support from AABB for travel during the conduct of the study. Dr Zantek reported receiving fees from the Association for the Advancement of Blood and Biotherapies for travel to a meeting for guideline development during the conduct of the study; that her spouse is an employee of Boston Scientific and has financial interest in the company and in ENDO International outside the submitted work; and serving on the board of directors for the American Society for Apheresis, BloodNet, External Quality Assurance in Thrombosis and Hemostasis, and the North American Specialized Coagulation Laboratory Association. No other disclosures were reported.

Funding/Support: Support for guideline development was provided by AABB, Bethesda, Maryland; and international partner organizations.

Additional Contributions: Maria-Helini Trivella, PhD (London School of Hygiene and Tropical Medicine), provided statistical advice without compensation. Panel and Guideline Group members: The panel included current or former members of the AABB Clinical Transfusion Medicine Committee (Jeffrey L. Carson, MD, Sara Bakhtary, MD, Claudia S. Cohn, MD, PhD, Brenda J. Grossman, MD, MPH, Gaurav K. Gupta, MD, PhD, Aaron S. Hess, MD, PhD, Jessica L. Jacobson, MD, Ryan A. Metcalf, MD, Colin H. Murphy, MD, Micah T. Prochaska, MD, Jay S. Raval, MD, Eric Salazar, MD, PhD, Nabih H. Saifee, MD, PhD, Aaron A. R. Tobian, MD, PhD, Jonathan Waters, MD, Nicole D. Zantek, MD, PhD, and Monica B. Pagano, MD) and members appointed by professional national and international organizations: Lewis J. Kaplan, MD (Society of Critical Care Medicine), Jonathan Waters, MD (American Society of Anesthesiologists and Society for Advancement of Patient Blood Management), Yulia Lin, MD (American Society of Hematology), Erica M. Wood, MD (International Society of Blood Transfusion), Cynthia So-Osman, MD, PhD (European Hematology Association), Katerina Pavenski, MD (International Collaboration for Transfusion Medicine Guidelines), and Stacey Valentine, MD, MPH (Pediatric Critical Care Transfusion and Anemia Expertise Initiative/Pediatric Critical Care Blood Research Network). Specialties represented included pathologists and hematologists (most with subspecialty expertise in transfusion medicine), anesthesiologists, pediatricians (Simon J. Stanworth, MD, DPhil, and Stacey Valentine, MD, MPH), internists (Jeffrey L. Carson, MD, and Micah T. Prochaska, MD), and critical care medicine physicians and trauma and acute care surgeons (Lewis J. Kaplan, MD). Chairs: Jeffrey L. Carson, MD, Department of Medicine, Rutgers Robert Wood Johnson Medical School; Chair, AABB CTMC committee: Monica B. Pagano, MD, Department of Laboratory Medicine and

Pathology, University of Washington; Simon J. Stanworth, MD, Department of Haematology, Oxford University Hospitals NHS Trust, NHSBT, and University of Oxford; Stacey Valentine, MD, Department of Pediatrics, UMASS Medical Center. Members: Sara Bakhtary, MD, Department of Laboratory Medicine, University of California–San Francisco, AABB CTMC member; Claudia S. Cohn, MD, PhD, Department of Laboratory Medicine and Pathology, University of Minnesota, AABB chief medical officer; Brenda J. Grossman, MD, MPH, Department of Pathology and Immunology, Washington University School of Medicine, AABB CTMC member; Gaurav K. Gupta, MD, PhD, Department of Pathology and Laboratory Medicine, Memorial Sloan Kettering Cancer Center, AABB CTMC member; Aaron S. Hess, MD, PhD, Departments of Anesthesiology and Pathology and Laboratory Medicine, University of Wisconsin–Madison, AABB CTMC member; Jessica L. Jacobson, MD, Department of Pathology, New York University Grossman School of Medicine and NYC Health + Hospitals/Bellevue, AABB CTMC member; Lewis J. Kaplan, MD, Department of Surgery, Division of Trauma, Surgical Critical Care and Surgical Emergencies, Perelman School of Medicine, University of Pennsylvania, Society of Critical Care Medicine, representative; Yulia Lin, MD, Precision Diagnostics and Therapeutics Program, Sunnybrook Health Sciences Centre, Department of Laboratory Medicine and Pathobiology, University of Toronto, American Society of Hematology, representative; Ryan A. Metcalf, MD, Department of Pathology, University of Utah, AABB CTMC member; Colin H. Murphy, MD, Pathology Associates of Albuquerque, Albuquerque, New Mexico, AABB CTMC member; Katerina Pavenski, MD, Department of Laboratory Medicine and Pathobiology, University of Toronto and St. Michael's Hospital–Unity Health Toronto, International Collaboration for Transfusion Medicine Guidelines, representative; Micah T. Prochaska, MD, Department of Medicine, University of Chicago, AABB CTMC member; Jay S. Raval, MD, Department of Pathology, University of New Mexico, AABB CTMC member; Eric Salazar, MD, PhD, Department of Pathology and Laboratory Medicine, UT Health San Antonio, AABB CTMC member; Nabih H. Saifee, MD, PhD, Department of Laboratory Medicine and Pathology, Seattle Children's Hospital, AABB CTMC member; Aaron A. R. Tobian, MD, PhD, Department of Pathology, Johns Hopkins University, AABB president-elect; Cynthia So-Osman, MD, PhD, Department of Unit Transfusion Medicine (UTG), Sanquin Blood Bank, Amsterdam, the Netherlands, Department of Hematology, Erasmus Medical Center, Rotterdam, the Netherlands, European Hematology Association SWG Transfusion, representative; Jonathan Waters, MD, Department of Anesthesiology and Perioperative Medicine, University of Pittsburgh, American Society of Anesthesiologists, representative, Society for Advancement of Patient Blood Safety, representative, AABB CTMC member; Erica M. Wood, MD, Department of Haematology, Monash Health, Monash University School of Public Health and Preventive Medicine, Melbourne, Victoria, Australia, International Society of Blood Transfusion, representative; Nicole D. Zantek, MD, PhD, Department of Laboratory Medicine and Pathology, University of Minnesota, AABB CTMC member. Patient partner: Allan Dubon, MLS,

ThermoFisher Scientific. Consultants: Gordon Guyatt, MD, Department of Clinical Epidemiology and Biostatistics and Department of Medicine, McMaster University; Jane Dennis, PhD, Cochrane Injuries Group, London School of Hygiene and Tropical Medicine. AABB staff: Sharon Carayannis, MT (ASCP)HP, vice president, Science and Practice; Ekaterina Torres, BS, meetings and awards manager.

REFERENCES

- World Health Organization. Blood transfusion. June 8, 2022. Accessed February 23, 2023. <https://www.who.int/news-room/facts-in-pictures/detail/blood-transfusion>
- Jones JM, Sapiano MRP, Mowla S, Bota D, Berger JJ, Basavaraju SV. Has the trend of declining blood transfusions in the United States ended? findings of the 2019 National Blood Collection and Utilization Survey. *Transfusion*. 2021;61 suppl 2 (suppl 2):S1-S10. doi:10.1111/trf.16449
- Hendrickson JE, Roubinian NH, Chowdhury D, et al; National Heart, Lung, and Blood Institute (NHLBI) Recipient Epidemiology and Donor Evaluation Study (REDS-III). Incidence of transfusion reactions: a multicenter study utilizing systematic active surveillance and expert adjudication. *Transfusion*. 2016;56(10):2587-2596. doi:10.1111/trf.13730
- Steele WR, Dodd RY, Notari EP, et al; Transfusion-Transmissible Infections Monitoring System (TTIMS). Prevalence of human immunodeficiency virus, hepatitis B virus, and hepatitis C virus in United States blood donations, 2015 to 2019: the Transfusion-Transmissible Infections Monitoring System (TTIMS). *Transfusion*. 2020;60(10):2327-2339. doi:10.1111/trf.16005
- Hibbs SP, Brunskill SJ, Donald GC, Saunders HD, Murphy MF. Setting priorities for research in blood donation and transfusion: outcome of the James Lind Alliance priority-setting partnership. *Transfusion*. 2019;59(2):574-581. doi:10.1111/trf.15077
- Mowla SJ, Sapiano MRP, Jones JM, Berger JJ, Basavaraju SV. Supplemental findings of the 2019 National Blood Collection and Utilization Survey. *Transfusion*. 2021;61 suppl 2 (suppl 2):S11-S35.
- Kacker S, Frick KD, Tobian AA. The costs of transfusion: economic evaluations in transfusion medicine, part 1. *Transfusion*. 2013;53(7):1383-1385. doi:10.1111/trf.12188
- Stokes EA, Wordsworth S, Staves J, et al. Accurate costs of blood transfusion: a microcosting of administering blood products in the United Kingdom National Health Service. *Transfusion*. 2018;58(4):846-853. doi:10.1111/trf.14493
- Stanworth SJ, New HV, Apelseth TO, et al. Effects of the COVID-19 pandemic on supply and use of blood for transfusion. *Lancet Haematol*. 2020;7(10):e756-e764. doi:10.1016/S2352-3026(20)30186-1
- Carson JL, Grossman BJ, Kleinman S, et al Red blood cell transfusion: a clinical practice guideline from the AABB. *Ann Intern Med*. 2012;157(1):49-58.
- Carson JL, Guyatt G, Heddle NM, et al. Clinical practice guidelines from the AABB: red blood cell transfusion thresholds and storage. *JAMA*. 2016;316(19):2025-2035. doi:10.1001/jama.2016.9185
- Valentine SL, Bembea MM, Muszynski JA, et al; Pediatric Critical Care Transfusion and Anemia Expertise Initiative (TAXI); Pediatric Critical Care Blood Research Network (BloodNet), and the Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network. Consensus recommendations for RBC transfusion practice in critically ill children from the Pediatric Critical Care Transfusion and Anemia Expertise Initiative. *Pediatr Crit Care Med*. 2018;19(9):884-898. doi:10.1097/PCC.0000000000001613
- Carson JL, Stanworth SJ, Dennis JA, et al. Transfusion thresholds for guiding red blood cell transfusion. *Cochrane Database Syst Rev*. 2021;12(12):CD002042.
- Shiffman RN. Recognizing trustworthy guidelines: the new IOM standards. Accessed January 2, 2023. https://www.cdc.gov/os/quality/docs/trustworthy_gls.pdf
- Guyatt GH, Oxman AD, Vist GE, et al; GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336(7650):924-926. doi:10.1136/bmj.39489.470347.AD
- AABB. AABB conflicts of interest disclosure form. Accessed February 23, 2023. <https://www.aabb.org/membership/governance/committees/Pages/AABB-Conflicts-of-Interest-Disclosure-Form.aspx>
- Wang P, Wang X, Deng H, et al. Restrictive versus liberal transfusion thresholds in very low birth weight infants: a systematic review with meta-analysis. *PLoS One*. 2021;16(8):e0256810. doi:10.1371/journal.pone.0256810
- Maitland K, Kiguli S, Olupot-Olupot P, et al; TRACT Group. Immediate transfusion in African children with uncomplicated severe anemia. *N Engl J Med*. 2019;381(5):407-419. doi:10.1056/NEJMoa1900105
- Maitland K, Olupot-Olupot P, Kiguli S, et al; TRACT Group. Transfusion volume for children with severe anemia in Africa. *N Engl J Med*. 2019;381(5):420-431. doi:10.1056/NEJMoa1900100
- Akyildiz B, Ulgen Tekerek N, Pamukcu O, et al. Comprehensive analysis of liberal and restrictive transfusion strategies in pediatric intensive care unit. *J Trop Pediatr*. 2018;64(2):118-125. doi:10.1093/tropej/fmx037
- Morton S, Sekhar M, Smethurst H, et al. Do liberal thresholds for red cell transfusion result in improved quality of life for patients undergoing intensive chemotherapy for acute myeloid leukemia? a randomized crossover feasibility study. *Haematologica*. 2022;107(6):1474-1478. doi:10.3324/haematol.2021.279867
- Salehi SH, Daniali M, Motaghi P, Momeni M. The best strategy for red blood cell transfusion in severe burn patients, restrictive or liberal: a randomized controlled trial. *Burns*. 2021;47(5):1038-1044. doi:10.1016/j.burns.2020.06.038
- Buckstein RJ, Prica A, Leber B, et al. RBC-Enhance: a randomized pilot feasibility trial of red cell transfusion thresholds in myelodysplastic syndromes. *Blood*. 2020;136(suppl 1):3. doi:10.1182/blood-2020-140165
- Higgins JP, Altman DG, Gøtzsche PC, et al; Cochrane Bias Methods Group; Cochrane Statistical Methods Group. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928. doi:10.1136/bmj.d5928
- Higgins J, Thomas J. *Cochrane Handbook for Systematic Reviews of Interventions*. Accessed January 2, 2023. <https://training.cochrane.org/handbook/current>
- Schandelmaier S, Briel M, Varadhan R, et al. Development of the instrument to assess the credibility of effect modification analyses (ICEMAN) in randomized controlled trials and meta-analyses. *CMAJ*. 2020;192(32):E901-E906.
- Review Manager 5 (RevMan 5): Version 5.4. Nordic Cochrane Centre, Cochrane Collaboration; 2020.
- Guyatt GH, Oxman AD, Santesso N, et al. GRADE guidelines, 12: preparing summary of findings tables—binary outcomes. *J Clin Epidemiol*. 2013;66(2):158-172. doi:10.1016/j.jclinepi.2012.01.012
- Atkins D, Best D, Briss PA, et al; GRADE Working Group. Grading quality of evidence and strength of recommendations. *BMJ*. 2004;328(7454):1490. doi:10.1136/bmj.328.7454.1490
- Guyatt GH, Oxman AD, Schünemann HJ, Tugwell P, Knottnerus A. GRADE guidelines: a new series of articles in the *Journal of Clinical Epidemiology*. *J Clin Epidemiol*. 2011;64(4):380-382. doi:10.1016/j.jclinepi.2010.09.011
- Alonso-Coello P, Oxman AD, Moberg J, et al; GRADE Working Group. GRADE evidence to decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices, 2: clinical practice guidelines. *BMJ*. 2016;353:i2089. doi:10.1136/bmj.i2089
- Webert KE, Cook RJ, Couban S, et al. A multicenter pilot-randomized controlled trial of the feasibility of an augmented red blood cell transfusion strategy for patients treated with induction chemotherapy for acute leukemia or stem cell transplantation. *Transfusion*. 2008;48(1):81-91.
- DeZern AE, Williams K, Zahurak M, et al. Red blood cell transfusion triggers in acute leukemia: a randomized pilot study. *Transfusion*. 2016;56(7):1750-1757. doi:10.1111/trf.13658
- Tay J, Allan DS, Chatelain E, et al. Liberal versus restrictive red blood cell transfusion thresholds in hematopoietic cell transplantation: a randomized, open label, phase III, noninferiority trial. *J Clin Oncol*. 2020;38(13):1463-1473. doi:10.1200/JCO.19.01836
- Lacroix J, Hébert PC, Hutchison JS, et al; TRIPICU Investigators; Canadian Critical Care Trials Group; Pediatric Acute Lung Injury and Sepsis Investigators Network. Transfusion strategies for patients in pediatric intensive care units. *N Engl J Med*. 2007;356(16):1609-1619. doi:10.1056/NEJMoa066240
- Laine A, Niemi T, Schramko A. Transfusion threshold of hemoglobin 80g/L is comparable to 100g/L in terms of bleeding in cardiac surgery: a prospective randomized study. *J Cardiothorac Vasc Anesth*. 2018;32(1):131-139. doi:10.1053/j.jvca.2017.08.039
- Gillies MA, Ghaffar S, Moppett IK, et al. A restrictive versus liberal transfusion strategy to prevent myocardial injury in patients undergoing surgery for fractured neck of femur: a feasibility randomised trial (RESULT-NOF). *Br J Anaesth*. 2021;126(1):77-86. doi:10.1016/j.bja.2020.06.048
- Gobatto ALN, Link MA, Solla DJ, et al. Transfusion requirements after head trauma: a randomized feasibility controlled trial. *Crit Care*. 2019;23(1):89-89. doi:10.1186/s13054-018-2273-9

39. Parker MJ. Randomised trial of blood transfusion versus a restrictive transfusion policy after hip fracture surgery. *Injury*. 2013;44(12):1916-1918. doi:10.1016/j.injury.2013.04.033
40. Hébert PC, Wells G, Marshall J, et al; Canadian Critical Care Trials Group. Transfusion requirements in critical care. A pilot study. [published erratum appears in *JAMA* 1995 Sep 27;274(12):944]. *JAMA*. 1995;273(18):1439-1444. doi:10.1001/jama.1995.03520420055038
41. de Almeida JP, Vincent JL, Galas FR, et al. Transfusion requirements in surgical oncology patients: a prospective, randomized controlled trial. *Anesthesiology*. 2015;122(1):29-38. doi:10.1097/ALN.0000000000000511
42. Palmieri TL, Holmes JH IV, Arnoldo B, et al. Transfusion requirement in burn care evaluation (TRIBE). A multicenter randomized prospective trial of blood transfusion in major burn injury. *Ann Surg*. 2017;266(4):595-602. doi:10.1097/SLA.0000000000002408
43. Walsh TS, Boyd JA, Watson D, et al; RELIEVE Investigators. Restrictive versus liberal transfusion strategies for older mechanically ventilated critically ill patients: a randomized pilot trial. *Crit Care Med*. 2013;41(10):2354-2363. doi:10.1097/CCM.0b013e318291cc4e
44. Murphy GJ, Pike K, Rogers CA, et al; TITRe2 Investigators. Liberal or restrictive transfusion after cardiac surgery. *N Engl J Med*. 2015;372(11):997-1008. doi:10.1056/NEJMoa1403612
45. Villanueva C, Colomo A, Bosch A, et al. Transfusion strategies for acute upper gastrointestinal bleeding. *N Engl J Med*. 2013;368(1):11-21. doi:10.1056/NEJMoa1211801
46. Mazer CD, Whitlock RP, Fergusson DA, et al; TRICS Investigators and Perioperative Anesthesia Clinical Trials Group. Restrictive or liberal red-cell transfusion for cardiac surgery. *N Engl J Med*. 2017;377(22):2133-2144. doi:10.1056/NEJMoa1711818
47. Hébert PC, Wells G, Blajchman MA, et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. *N Engl J Med*. 1999;340(6):409-417. doi:10.1056/NEJM199902113400601
48. Bergamin FS, Almeida JP, Landoni G, et al. Liberal versus restrictive transfusion strategy in critically ill oncologic patients: the transfusion requirements in critically ill oncologic patients: randomized controlled trial. *Crit Care Med*. 2017;45(5):766-773. doi:10.1097/CCM.0000000000002283
49. Holst LB, Haase N, Wetterslev J, et al; TRISS Trial Group; Scandinavian Critical Care Trials Group. Lower versus higher hemoglobin threshold for transfusion in septic shock. *N Engl J Med*. 2014;371(15):1381-1391. doi:10.1056/NEJMoa1406617
50. Lotte PA, Barth P, Garino JP, Cook EF. Predonated autologous blood transfusions after total knee arthroplasty: immediate versus delayed administration. *J Arthroplasty*. 1999;14(6):647-650. doi:10.1016/S0883-5403(99)90216-4
51. Grover M, Talwalkar S, Casbard A, et al. Silent myocardial ischaemia and haemoglobin concentration: a randomized controlled trial of transfusion strategy in lower limb arthroplasty. *Vox Sang*. 2006;90(2):105-112. doi:10.1111/j.1423-0410.2006.00730.x
52. Blair SD, Janvrin SB, McCollum CN, Greenhalgh RM. Effect of early blood transfusion on gastrointestinal haemorrhage. *Br J Surg*. 1986;73(10):783-785. doi:10.1002/bjs.1800731007
53. Foss NB, Kristensen MT, Jensen PS, Palm H, Krashennikoff M, Kehlet H. The effects of liberal versus restrictive transfusion thresholds on ambulation after hip fracture surgery. *Transfusion*. 2009;49(2):227-234. doi:10.1111/j.1537-2995.2008.01967.x
54. Carson JL, Terrin ML, Barton FB, et al. A pilot randomized trial comparing symptomatic vs. hemoglobin-level-driven red blood cell transfusions following hip fracture. *Transfusion*. 1998;38(6):522-529. doi:10.1046/j.1537-2995.1998.38698326331.x
55. Møller A, Nielsen HB, Wetterslev J, et al. Low vs high hemoglobin trigger for transfusion in vascular surgery: a randomized clinical feasibility trial. *Blood*. 2019;133(25):2639-2650. doi:10.1182/blood-2018-10-877530
56. Webert KE, Cook RJ, Couban S, et al. A multicenter pilot-randomized controlled trial of the feasibility of an augmented red blood cell transfusion strategy for patients treated with induction chemotherapy for acute leukemia or stem cell transplantation. *Transfusion*. 2008;48(1):81-91.
57. Cooper HA, Rao SV, Greenberg MD, et al. Conservative versus liberal red cell transfusion in acute myocardial infarction (the CRIT Randomized Pilot Study). *Am J Cardiol*. 2011;108(8):1108-1111. doi:10.1016/j.amjcard.2011.06.014
58. Carson JL, Brooks MM, Abbott JD, et al. Liberal versus restrictive transfusion thresholds for patients with symptomatic coronary artery disease. *Am Heart J*. 2013;165(6):964-971.e1. doi:10.1016/j.ahj.2013.03.001
59. Bush RL, Pevac WC, Holcroft JW. A prospective, randomized trial limiting perioperative red blood cell transfusions in vascular patients. *Am J Surg*. 1997;174(2):143-148. doi:10.1016/S0002-9610(97)00073-1
60. Hajjar LA, Vincent JL, Galas FR, et al. Transfusion requirements after cardiac surgery: the TRACS randomized controlled trial. *JAMA*. 2010;304(14):1559-1567. doi:10.1001/jama.2010.1446
61. Gregersen M, Borris LC, Damsgaard EM. Postoperative blood transfusion strategy in frail, anemic elderly patients with hip fracture: the TRIFE randomized controlled trial. *Acta Orthop*. 2015;86(3):363-372. doi:10.3109/17453674.2015.1006980
62. Jairath V, Kahan BC, Gray A, et al. Restrictive versus liberal blood transfusion for acute upper gastrointestinal bleeding (TRIGGER): a pragmatic, open-label, cluster randomised feasibility trial. *Lancet*. 2015;386(9989):137-144. doi:10.1016/S0140-6736(14)61999-1
63. Ducrocq G, Gonzalez-Juanatey JR, Puymirat E, et al; REALITY Investigators. Effect of a restrictive vs liberal blood transfusion strategy on major cardiovascular events among patients with acute myocardial infarction and anemia: the REALITY randomized clinical trial. *JAMA*. 2021;325(6):552-560. doi:10.1001/jama.2021.0135
64. Carson JL, Terrin ML, Noveck H, et al; FOCUS Investigators. Liberal or restrictive transfusion in high-risk patients after hip surgery. *N Engl J Med*. 2011;365(26):2453-2462. doi:10.1056/NEJMoa1012452
65. Carson JL. Myocardial Ischemia and Transfusion (MINT). National Library of Medicine. Accessed January 7, 2023. <https://clinicaltrials.gov/ct2/show/NCT02981407?term=NCT02981407&rank=1>
66. Robitaille N, Lacroix J, Alexandrov L, et al. Excess of veno-occlusive disease in a randomized clinical trial on a higher trigger for red blood cell transfusion after bone marrow transplantation: a Canadian Blood and Marrow Transplant Group trial. *Biol Blood Marrow Transplant*. 2013;19(3):468-473. doi:10.1016/j.bbmt.2012.12.002
67. Cholette JM, Powers KS, Alfieri GM, et al. Transfusion of cell saver salvaged blood in neonates and infants undergoing open heart surgery significantly reduces RBC and coagulant product transfusions and donor exposures: results of a prospective, randomized, clinical trial. *Pediatr Crit Care Med*. 2013;14(2):137-147. doi:10.1097/PCC.0b013e31826e741c
68. Cholette JM, Swartz MF, Rubenstein J, et al. Outcomes using a conservative versus liberal red blood cell transfusion strategy in infants requiring cardiac operation. *Ann Thorac Surg*. 2017;103(1):206-214. doi:10.1016/j.athoracsur.2016.05.049
69. de Gast-Bakker DH, de Wilde RB, Hazekamp MG, et al. Safety and effects of two red blood cell transfusion strategies in pediatric cardiac surgery patients: a randomized controlled trial. *Intensive Care Med*. 2013;39(11):2011-2019. doi:10.1007/s00134-013-3085-7
70. Vuille-Lessard E, Boudreault D, Girard F, Ruel M, Chagnon M, Hardy JF. Red blood cell transfusion practice in elective orthopedic surgery: a multicenter cohort study. *Transfusion*. 2010;50(10):2117-2124. doi:10.1111/j.1537-2995.2010.02697.x
71. Heddle NM, Cook RJ, Arnold DM, et al. Effect of short-term vs long-term blood storage on mortality after transfusion. *N Engl J Med*. 2016;375(20):1937-1945. doi:10.1056/NEJMoa1609014
72. Cooper DJ, McQuilten ZK, Nichol A, et al; TRANSFUSE Investigators and the Australian and New Zealand Intensive Care Society Clinical Trials Group. Age of red cells for transfusion and outcomes in critically ill adults. *N Engl J Med*. 2017;377(19):1858-1867. doi:10.1056/NEJMoa1707572
73. Hamm CW, Bassand JP, Agewall S, et al; ESC Committee for Practice Guidelines. ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: the Task Force for the Management of Acute Coronary Syndromes (ACS) in Patients Presenting Without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2011;32(23):2999-3054. doi:10.1093/eurheartj/ehr236
74. Ferraris VA, Brown JR, Despotis GJ, et al; Society of Thoracic Surgeons Blood Conservation Guideline Task Force; Society of Cardiovascular Anesthesiologists Special Task Force on Blood Transfusion; International Consortium for Evidence Based Perfusion. 2011 Update to the Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists blood conservation clinical practice guidelines. *Ann Thorac Surg*. 2011;91(3):944-982. doi:10.1016/j.athoracsur.2010.11.078

75. Retter A, Wyncoll D, Pearse R, et al; British Committee for Standards in Haematology. Guidelines on the management of anaemia and red cell transfusion in adult critically ill patients. *Br J Haematol*. 2013;160(4):445-464. doi:10.1111/bjh.12143
76. Rogers GM, Cela D, Cleeland C, et al. NCCN Guidelines Version 2.2014, Cancer- and Chemotherapy-Induced Anemia: NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). National Comprehensive Cancer Network; 2013.
77. American Society of Anesthesiologists Task Force on Perioperative Blood Management. Practice guidelines for perioperative blood management: an updated report by the American Society of Anesthesiologists Task Force on Perioperative Blood Management. *Anesthesiology*. 2015;122(2):241-275. doi:10.1097/ALN.0000000000000463
78. Qaseem A, Humphrey LL, Fitterman N, Starkey M, Shekelle P; Clinical Guidelines Committee of the American College of Physicians. Treatment of anemia in patients with heart disease: a clinical practice guideline from the American College of Physicians. *Ann Intern Med*. 2013;159(11):770-779. doi:10.7326/0003-4819-159-11-201312030-00009
79. Alexander J, Cifu AS. Transfusion of red blood cells. *JAMA*. 2016;316(19):2038-2039. doi:10.1001/jama.2016.12870
80. Kozek-Langenecker SA, Ahmed AB, Afshari A, et al. Management of severe perioperative bleeding: guidelines from the European Society of Anaesthesiology: first update 2016. *Eur J Anaesthesiol*. 2017;34(6):332-395. doi:10.1097/EJA.0000000000000630
81. Mueller MM, Van Remoortel H, Meybohm P, et al; ICC PBM Frankfurt 2018 Group. Patient blood management: recommendations from the 2018 Frankfurt Consensus Conference. *JAMA*. 2019;321(10):983-997. doi:10.1001/jama.2019.0554
82. Raphael J, Mazer CD, Subramani S, et al. Society of Cardiovascular Anesthesiologists clinical practice improvement advisory for management of perioperative bleeding and hemostasis in cardiac surgery patients. *J Cardiothorac Vasc Anesth*. 2019;33(11):2887-2899. doi:10.1053/j.jvca.2019.04.003
83. Tibi P, McClure RS, Huang J, et al. STS/SCA/AmSECT/SABM update to the clinical practice guidelines on patient blood management. *Ann Thorac Surg*. 2021;112(3):981-1004. doi:10.1016/j.athoracsur.2021.03.033