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Red Blood Cell Transfusion
2023 AABB International Guidelines

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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.

Viewpoint

Supplemental content

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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.

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.

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 recommendations[15] 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 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 models[28] 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.

[a] Downgraded for inconsistency.

[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.

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.

[a] Two downgrades for very serious 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 absolute difference = 4.1% more (4.2 fewer and 39.7 more).

[c] Imprecision.

[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 hemodynamically 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

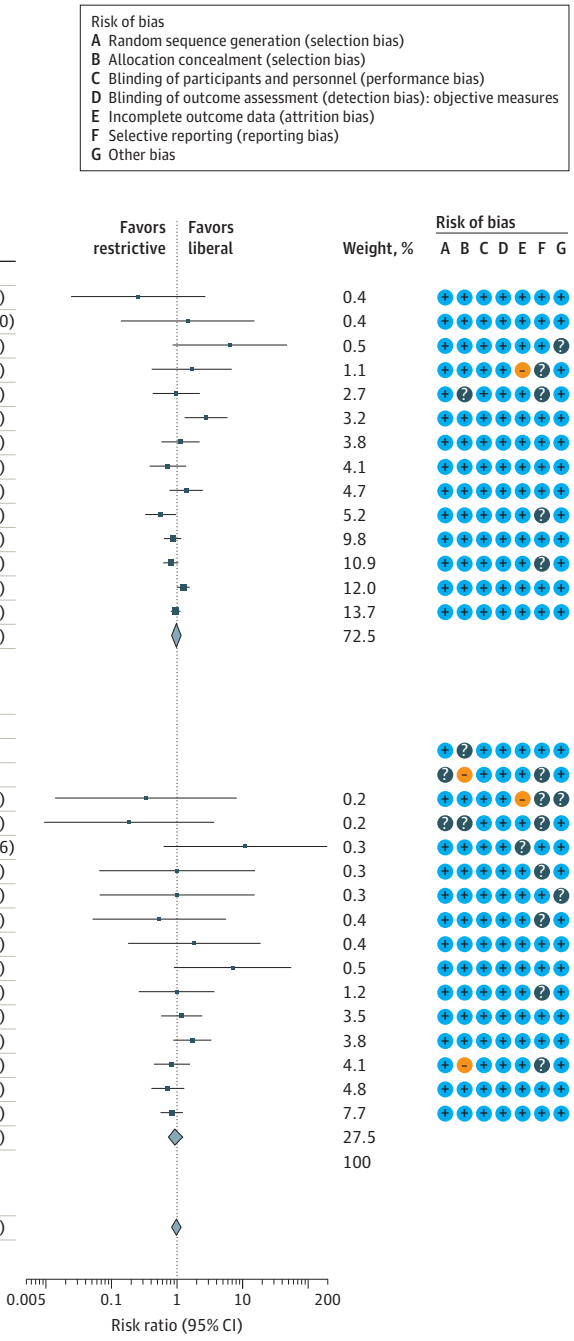

Figure modified from the Cochrane review [13] by removing 1 trial performed with pediatric patients (Lacroix et al[35]) and placing a second trial (Laine et al[36]) in the correct subgroup. Relative risks and the corresponding 95% CIs were calculated for each outcome with random-effects models unless 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 strategies[79-83] (**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.

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

Conclusion

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

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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 for 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 Americas, 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.

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