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Red Blood Cell Transfusion: A Clinical Practice Guideline From the AABB*

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Description: Although approximately 85 million units of red blood cells (RBCs) are transfused annually worldwide, transfusion practices vary widely. The AABB (formerly, the American Association of Blood Banks) developed this guideline to provide clinical recommendations about hemoglobin concentration thresholds and other clinical variables that trigger RBC transfusions in hemodynamically stable adults and children.

Methods: These guidelines are based on a systematic review of randomized clinical trials evaluating transfusion thresholds. We performed a literature search from 1950 to February 2011 with no language restrictions. We examined the proportion of patients who received any RBC transfusion and the number of RBC units transfused to describe the effect of restrictive transfusion strategies on RBC use. To determine the clinical consequences of restrictive transfusion strategies, we examined overall mortality, nonfatal myocardial infarction, cardiac events, pulmonary edema, stroke, thromboembolism, renal failure, infection, hemorrhage, mental confusion, functional recovery, and length of hospital stay.

Recommendation 1: The AABB recommends adhering to a restrictive transfusion strategy (7 to 8 g/dL) in hospitalized, stable patients (Grade: strong recommendation; high-quality evidence).

Recommendation 2: The AABB suggests adhering to a restrictive strategy in hospitalized patients with preexisting cardiovascular disease and considering transfusion for patients with symptoms or a hemoglobin level of 8 g/dL or less (Grade: weak recommendation; moderate-quality evidence).

Recommendation 3: The AABB cannot recommend for or against a liberal or restrictive transfusion threshold for hospitalized, hemodynamically stable patients with the acute coronary syndrome (Grade: uncertain recommendation; very low-quality evidence).

Recommendation 4: The AABB suggests that transfusion decisions be influenced by symptoms as well as hemoglobin concentration (Grade: weak recommendation; low-quality evidence).

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Approximately 15 million red blood cell (RBC) units are transfused annually in the United States (1); about 85 million are transfused annually worldwide (2). Although there are many potential reasons for the different RBC transfusion practices that exist throughout the world, one reason may be the limited high-quality evidence of the benefits and harms of RBC transfusions.

Physicians most commonly use hemoglobin concentration to decide when to transfuse (3). However, most guidelines (4, 5) emphasize that transfusion should be given for symptoms of anemia and should not be based on hemoglobin concentration alone.

Previous guidelines have identified patients with coronary artery disease as an important subgroup that may need to be treated differently. Oxygen delivery from RBCs to the heart is critical and may be reduced by obstructed coronary arteries or anemia. Animal (6–8) and human (9) studies indicate higher risk for death and complications associated with anemia in the presence of coronary artery disease. Hence, there is concern about withholding RBC transfusion in patients with ischemic cardiovascular disease.

Optimal use should involve administering enough RBCs to maximize clinical outcomes while avoiding unnecessary transfusions that increase costs and expose patients to potential infectious or noninfectious risks. The **Figure** depicts amounts of such risks and, to provide context, contrasts those amounts with other risks, such as motor vehicle fatalities. Because there is no reason to transfuse more RBCs unless doing so improves outcomes, a liberal transfusion strategy (use of higher hemoglobin thresholds) would be preferable only if evidence supports its superior-

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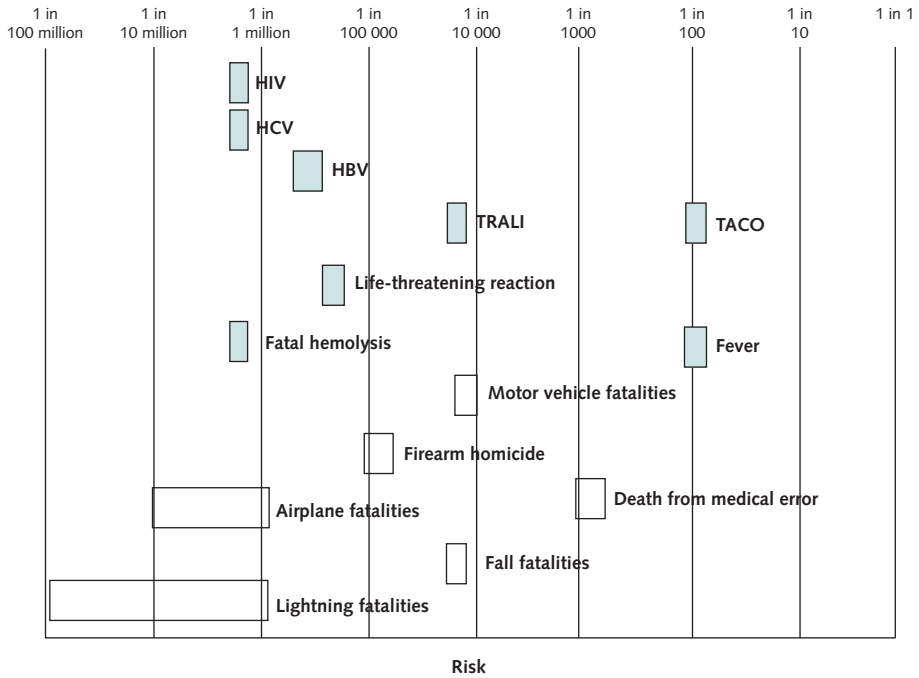
* These guidelines were prepared by a work group representing the following organizations: UMDNJ–Robert Wood Johnson Medical School, Roswell Park Cancer Institute, Fletcher Allen Health Care, Washington University School of Medicine, University of Texas Medical Center at Houston, U.S. Food and Drug Administration, Yale Medical Group, University of Iowa, University of British Columbia, University of Alabama at Birmingham, American Red Cross, Duke University School of Medicine, Emory University School of Medicine, Englewood Hospital and Medical Center, Ottawa Hospital Research Institute, Johns Hopkins University School of Medicine, University of Massachusetts Medical School, H. Lee Moffitt Cancer Center and Research Institute, Cedars Sinai Medical Center, and AABB. For members of the work group, see **Appendix 1** (available at www.annals.org).

Figure. **Adverse effects of RBC transfusion contrasted with other risks.**



Risk is depicted on a logarithmic scale. Shaded bars represent the risk per RBC unit transfused, and unshaded bars represent the risk for fatality per person per year for various life events. During 2007 through 2008, HIV incidence in blood donors was 3.1 per 100 000 person-years. Residual risk was estimated as 1:1 467 000 transfused blood components or 6.8 per 10 million transfused components (10). During 2007 through 2008, HCV incidence in blood donors was 5.1 per 100 000 person-years with residual risk estimate of 0.87 per million transfused blood components (1:1 149 000) or 8.7 per 10 million transfused components (10). For 2006 to 2008, HBV incidence in blood donors was 3.41 to 3.43 per 100 000 person-years. The estimated residual risk for HBV was 1 in 282 000 to 1 in 357 000 transfused blood components (11) or 2.8 per million to 3.6 per million transfused blood components. In a recently published, large, prospective study with active recipient surveillance, the rate of TRALI occurrence in 2009 was 0.81 (95% CI, 0.44 to 1.49) per 10 000 transfused blood components or 8.1 per 100 000 transfused blood components (12). Although the literature has a wide range of TRALI risk estimates (1, 13–16), we have selected the rate reported in this recent prospective study. Three studies of TACO have produced similar results. In a study of 901 intensive care unit patients, 6% of patients who received transfusions developed TACO. Median units transfused were 2 RBCs and 3 overall (including plasma and platelets) (17). The rate per transfused RBC unit was 2 to 3 per 100. In 382 patients undergoing hip and knee replacement, 1% developed TACO after surgery (18). In a study of patients having total hip and knee arthroplasty, 8% developed fluid overload necessitating diuretic use and 4% of patients who did not receive transfusions developed fluid overload, leading to a TACO estimate of 4% (19). In published studies from the late 1990s, the risk for fatal hemolysis was estimated to range from 1.3 to 1.7 per million (5.9 to 7.7 per 10 million) transfused RBC units in one report (20) and 1 per 1 800 000 or 8.5 per 10 million in a second report (21). More recently, transfusion-related fatalities due to hemolysis reported to the U.S. Food and Drug Administration averaged 12.5 deaths per year from 2005 to 2010 (22). With 15 million RBC units transfused per year, the estimated risk for death due to hemolysis is 1:1 250 000 or 8 per 10 million RBC units. Fever (febrile nonhemolytic transfusion reactions) was estimated to be 1.1% with prestorage leukoreduction and 2.15% with poststorage leukoreduction (23). Death from medical error as reported by the Institute of Medicine was 1.3 to 2.9 per 1000 hospital admissions (24). Life-threatening transfusion reactions, defined as reactions requiring major medical intervention (for example, vasopressors, intubation, or transfer to an intensive care unit), occurred in 1:139 908 transfusions or 7.1 per million transfusions (1). Fatal motor vehicle accidents were estimated at 13.1 per 100 000 persons in 2008 or 1.3 per 10 000 persons (25). The rate of firearm homicide (which excludes suicide) was 4 per 100 000 persons in 2008 (25). Fatal falls were estimated at 8.2 deaths per 100 000 persons in 2008 (25). Lightning fatalities ranged from 0.02 per million (2 per 100 million) persons in California and Massachusetts to 2.0 per million persons in Wyoming (0 risk in Hawaii, Rhode Island, and Alaska) (26). The odds of being killed on a single airline flight on the 30 airlines with the best accident rates were 1 per 29.4 million. Among the 25 airlines with the worst accident records, rates were 1.7 per million per flight (27). Modified from Dzik (2002) (28). HBV = hepatitis B virus; HCV = hepatitis C virus; RBC = red blood cell; TACO = transfusion-associated circulatory overload; TRALI = transfusion-related acute lung injury.

ity over a restrictive transfusion strategy (use of lower hemoglobin thresholds). Thus, restrictive transfusion is preferable if reliable evidence demonstrates either noninferiority or superiority to liberal transfusion.

Many small trials have addressed the question of optimal use of RBC transfusions. Two reviews of the Cochrane database, including an update in 2010 that included all available trials published through August 2009, have summarized those data (29, 30). Recently, 2 additional trials were published that expanded by 30% the number of patients included in the evidence base of transfusion trials (31, 32). Thus, it is timely to reexamine the data and provide guidance to the medical community.

Guideline Focus

These guidelines focus on hemoglobin concentration thresholds and other clinical variables that might trigger RBC transfusion. Practice guidelines are not intended as standards or absolute requirements and do not apply to all

individual transfusion decisions. Clinical judgment is critical in the decision to transfuse; therefore, transfusing RBCs above or below the specified hemoglobin threshold may be dictated by the clinical context. Similarly, the decision not to transfuse RBCs to a patient with a hemoglobin concentration below the recommended thresholds is also a matter of clinical judgment.

TARGET POPULATION

These guidelines provide advice for hemodynamically stable adults and children who are candidates for RBC transfusions.

GUIDELINE DEVELOPMENT PROCESS

The AABB (formerly, the American Association of Blood Banks) commissioned and funded these guidelines through the AABB Clinical Transfusion Medicine Committee. In addition, the AABB Board of Directors directed the committee to recruit experts with interest in RBC transfusion from other professional organizations.

Panel Composition

A committee of 20 experts was assembled. Twelve were current or former members of the AABB Clinical Transfusion Medicine Committee, whereas 6 were appointed by their respective professional organizations as subject matter experts. Fifteen of the physicians were pathologists or hematologists, most of whom had subspecialty expertise in transfusion medicine. The others included an anesthesiologist; a cardiologist; a pediatrician; experts in critical care medicine; trauma surgeons; specialists in internal medicine and systematic review; and a Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodologist. Committee members had no substantial conflicts of interest as defined by the AABB conflict of interest policy (33). Pursuant to the policy, individual members were required to disclose actual and apparent financial, professional, or personal conflicts.

Evidence Review and Grading

Systematic Review

We developed these guidelines on the basis of an updated systematic review of the literature on transfusion thresholds, which is separately published by the first author of this paper (30, 34). We searched the Cochrane Injuries Group Specialized Register, CENTRAL (Cochrane Central Register of Controlled Trials), MEDLINE from 1950 to the second week of August 2009, EMBASE from 1980 to the fourth week of 2011, SCI-EXPANDED (Science Citation Index Expanded) from 1970 to February 2011, and CPCI-S (Conference Proceedings Citation Index-Science) from 1990 to February 2011. There were no language restrictions. We received no external funding.

The systematic review included randomized, controlled trials in which the transfusion groups were assigned on the basis of a clear transfusion "trigger" or "threshold," described as the hemoglobin level or hematocrit that had to be reached before transfusion of RBCs. Comparison group patients were required to have received transfusions with allogeneic or autologous RBCs at higher hemoglobin levels or hematocrits (transfusion threshold) than the intervention group. Alternatively, the control group could have received transfusions in accordance with current transfusion practices, which may not have included a well-defined threshold but involved liberal rather than restrictive transfusion practices. We included trials of surgical and medical patients involving adults and children. We did not examine adverse events related to transfusion. We also did not examine observational studies evaluating the effect of transfusion because such studies are especially prone to confounding by indication and may give biased results (35, 36).

The primary outcomes in the systematic review were the proportion of patients who received transfusions with allogeneic or autologous RBCs. Secondary outcomes included illness (nonfatal myocardial infarction, cardiac events, pulmonary edema, congestive heart failure, stroke, thromboembolism, renal failure, infection, hemorrhage, mental confusion), death, hemoglobin levels (postoperative or postdischarge), length of hospital stay, and the number of units transfused.

We evaluated each clinical trial for the risk of bias in sequence generation, allocation concealment, blinding, and incomplete outcome data by using methods recommended by the Cochrane Collaboration (37). We examined statistical heterogeneity by using both the I^2 and chi-square tests (37). We performed all analyses by using Cochrane Collaboration Review Manager Software (The Nordic Cochrane Center, Copenhagen, Denmark). For each trial, we calculated the relative risk (RR) for allogeneic transfusion in the intervention group compared with the control group and the corresponding 95% CI by using the random-effects model (38).

Grading of Evidence

We used the GRADE methodology to develop these guidelines (39, 40) (**Appendix 2**, available at www.annals.org). We prepared evidence profiles that display information on the effect of RBC transfusion in terms of benefits and harms for the most important clinical outcomes. The profiles also contained information on study limitations, consistency, directness, precision, and reporting bias. For each question or indication, the panel rated the importance of each outcome in influencing the decision to administer a transfusion to a patient. The outcomes were scored from 1 (not critical to making a decision) to 9 (critical to making a decision). The panel also rated the quality of evidence across all outcomes. The overall quality of the trials for each outcome was first assessed by 2 of the authors, after which a consensus of the entire panel was adopted. Each member of the panel was asked to make his or her final

Table 1. **Evidence Tables for Transfusion Outcomes**

Studies, *n* (References)	Quality Assessment*					
	Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations
Patients exposed to blood transfusion (all studies)						
17 (31, 32, 41–45, 47–56)	Randomized trials	No serious risk of bias	No serious inconsistency†	No serious indirectness	No serious imprecision	None
Units of blood transfused						
8 (41–43, 50–52, 54, 55)	Randomized trials	No serious risk of bias	No serious inconsistency†	No serious indirectness	No serious imprecision	None
Hemoglobin concentration						
12 (31, 32, 41, 43–46, 48, 50, 52, 54, 55)	Randomized trials	No serious risk of bias	No serious inconsistency†	No serious indirectness	No serious imprecision	None

* Quality assessment evaluates risk of bias, inconsistency (based on heterogeneity among trials), indirectness (based on assessment of generalizability of results), and imprecision (based on width of CIs).
† Large statistical heterogeneity was detected for red blood cell transfusion outcome. This is a reflection of the expected clinical heterogeneity because the 2 testing strategies were compared across many clinical settings (surgery [cardiac, vascular, orthopedic]: 8 randomized, controlled trials; trauma and blood loss: 5 randomized, controlled trials; intensive care unit: 3 randomized, controlled trials; and stem cell transplantation for acute leukemia: 1 randomized, controlled trial), with transfusion triggers differing among trials, and age of patients varying from approximately 45 y to greater than 80 y. However, the results remained consistent across all settings and patient populations (effect size differed, but no reversal in direction of effect was seen), indicating the robustness of the findings.

judgment on the strength of each recommendation and the overall quality of the body of evidence. The final quality rating and the strength of each recommendation were reached by consensus during an in-person meeting with the panel members.

Comments and Modification

The first author prepared the draft guideline document, which was modified and approved by all panel members and the AABB Clinical Transfusion Medicine Committee. Subsequently, the AABB Board of Directors reviewed and approved the guidelines.

CLINICAL RECOMMENDATIONS

Question 1

In hospitalized, hemodynamically stable patients, at what hemoglobin concentration should a decision to transfuse RBCs be considered?

Recommendations

The AABB recommends adhering to a restrictive transfusion strategy.

In adult and pediatric intensive care unit patients, transfusion should be considered at hemoglobin concentrations of 7 g/dL or less.

In postoperative surgical patients, transfusion should be considered at a hemoglobin concentration of 8 g/dL or less or for symptoms (chest pain, orthostatic hypotension or tachycardia unresponsive to fluid resuscitation, or congestive heart failure).

Quality of evidence: high; strength of recommendation: strong.

Evidence Summary

Nineteen trials ($n = 6264$ patients) meeting the inclusion criteria were identified (31, 32, 41–57). Transfusion outcomes are summarized in **Table 1**. Overall, 39% fewer patients received transfusions in the restrictive group than in the liberal group. The mean number of units of RBCs transfused was 1.19 units lower and the mean hemoglobin concentration before transfusion was 1.48 g/dL lower in the restrictive group. These findings confirm that a restrictive transfusion strategy leads to a clinically important reduction in RBC use and a lower mean hemoglobin concentration.

The effect of restrictive transfusion on clinical outcomes is described in **Table 2**. Thirty-day mortality was reported in 11 of 19 clinical trials (31, 32, 41–44, 47, 49, 50, 52, 53). The risk of bias was low for this outcome. Restrictive transfusion resulted in lower mortality than did liberal transfusion (RR, 0.85 [95% CI, 0.7 to 1.03]), although the finding was not statistically significant. The upper limit of the CI suggests that a liberal transfusion strategy is unlikely to result in a clinically important reduction in mortality. The ability to walk independently or length of hospital stay did not differ between the 2 groups. For all other outcomes that were evaluated, we found no evidence to suggest that patients were harmed by a restrictive transfusion strategy, although many of the outcomes evaluated were infrequent and a true difference between the groups may have been undetectable.

Rationale for Recommendations

Our recommendation is based on the evidence that restrictive transfusion is safe and associated with less blood

Table 1—Continued

Patients, *n/N*		Effect		Quality	Importance
Restrictive Transfusion Strategy	Liberal Transfusion Strategy	Relative Risk (95% CI)	Absolute Effect		
1416/3059 (46.3%)	2575/3066 (84.0%)	0.61 (0.52 to 0.72)	Risk reduction, 328 fewer per 1000 (235 fewer to 403 fewer)	High	Important
1357	1358	–	Mean difference, −1.19 (−1.85 to −0.53)	High	Important
2653	2649	–	Mean difference, −1.48 (−1.92 to −1.03)	High	Important

use. Although transfusion triggers differed among trials, no results favored the liberal strategy; in fact, the 3 largest trials conclusively showed a lack of benefit with liberal transfusion. Therefore, it is unlikely that a beneficial effect of liberal transfusion was missed. Our choice of the specific hemoglobin triggers is based on results from individual trials. The recommendation of 7 g/dL in adult and pediatric intensive care unit patients is based on the TRICC (Transfusion Requirements in Critical Care) (50) and TRIPICU (Transfusion Strategies for Patients in Pediatric Intensive Care Units) (52) trials, in which 7 g/dL was the hemoglobin level used in the restrictive group. The recommendation of 8 g/dL or symptoms in postoperative surgical patients is based on the results of the FOCUS (Transfusion Trigger Trial for Functional Outcomes in Cardiovascular Patients Undergoing Surgical Hip Fracture Repair) trial (32). The restrictive strategy in this trial permitted transfusion if the postoperative hemoglobin concentration was less than 8 g/dL or if the patient had symptoms, defined as chest pain believed to be cardiac in origin, orthostatic hypotension or tachycardia unresponsive to fluid challenge, or congestive heart failure. The panel believed that these recommendations would probably apply to most postsurgical and medical patients, with the exception of those with the acute coronary syndrome. We also recommend restrictive transfusion in patients receiving predeposit, autologous RBCs.

Whether surgical or medical patients outside the critical care setting would tolerate hemoglobin concentrations to 7 g/dL, similar to intensive care unit patients, has not been directly evaluated. Also, these recommendations do not address preoperative transfusion because this decision must also consider expected blood loss associated with the surgical procedure.

Question 2

In hospitalized, hemodynamically stable patients with preexisting cardiovascular disease, at what hemoglobin concentration should a decision to transfuse RBCs be considered?

Recommendations

The AABB suggests adhering to a restrictive transfusion strategy.

Transfusion should be considered at a hemoglobin concentration of 8 g/dL or less or for symptoms (chest pain, orthostatic hypotension or tachycardia unresponsive to fluid resuscitation, or congestive heart failure).

Quality of evidence: moderate; strength of recommendation: weak.

Evidence Summary

Clinical trial data that directly address the subgroup of patients with underlying cardiovascular disease are limited. The FOCUS trial (32) included postoperative patients with cardiovascular disease and cardiovascular risk factors. Overall, there was no difference in functional recovery; mortality; or hospital complications of myocardial infarction, congestive heart failure, stroke, infection, or thromboembolism with a liberal or restrictive transfusion strategy. Although 63% of patients had coronary artery disease or cardiovascular disease, the published results do not provide findings in the subgroup of patients with cardiovascular disease only or in patients with coronary artery disease. The only exception was for the primary outcomes of walking independently or death at 60 days; there was no difference (RR, 0.99 [CI, 0.88 to 1.11]) (32) in outcomes between the 2 strategies, nor in results comparing patients who had cardiovascular disease with patients who had cardiovascular risk factors only. In the TRICC trial (50), 43% of patients had cardiovascular disease. A subgroup analysis of these patients found that mortality rates were identical but there was a trend toward increased mortality in patients with ischemic heart disease in the restrictive transfusion group.

Two trials comparing the risk for myocardial infarction from restrictive transfusion and liberal transfusion provided 60% of the data. The TRICC trial found a lower

Table 2. **Evidence Tables for Clinical Outcomes**

Studies (References)	Quality Assessment*					
Variable	**Design**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other Considerations**
Thirty-day mortality (follow-up, 0–30 d; assessed with: Direct observation or telephone follow-up)						
11 (31, 32, 41–44, 47, 49, 50, 52, 53)	Randomized trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None
Myocardial infarction (assessed with: Systematic screening or clinical detection†)						
8 (32, 42, 43, 47, 48, 50, 51, 53)	Randomized trials	No serious risk of bias	Serious‡	No serious indirectness	Serious§	None
Pulmonary edema or congestive heart failure (assessed with: Clinically recognized)						
5 (32, 47, 50–52)	Randomized trials	Serious‖	Serious¶	No serious indirectness	No serious imprecision	None
Cerebrovascular accident (stroke) (assessed with: Clinically recognized)						
5 (31, 32, 44, 47, 51)	Randomized trials	Serious‖	No serious inconsistency	No serious indirectness	No serious imprecision	None
Thromboembolism (assessed with: Objective testing)						
3 (32, 44, 47)	Randomized trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious§	None
Infection (assessed with: Clinically recognized)						
6 (31, 32, 42, 47, 52, 54)	Randomized trials	Serious‖	No serious inconsistency	No serious indirectness	No serious imprecision	None
Inability to walk or death at 60 d (mean follow-up, 60 d; assessed with: Telephone follow-up)						
1 (32)	Randomized trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious**	None
Hospital length of stay (better indicated by lower values; assessed with: Direct observation)						
8 (32, 42–44, 47, 50, 51, 54)	Randomized trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None

* Quality assessment evaluates risk of bias, inconsistency (based on heterogeneity among trials), indirectness (based on assessment of generalizability of results), and imprecision (based on width of CIs).
† Most events were reported by Carson and colleagues (32). Participants in this study had 4 protocol-directed troponin levels and 3 electrocardiograms at specified time points, the results of which were evaluated to screen for events and central blinded classification of acute myocardial infarction.
‡ Two of the largest trials (Carson and colleagues [32] and Hébert and colleagues [49]) had inconsistent results (see text for details).
§ Low event rates with wide CIs.
‖ Clinically recognized and unblinded assessment.
¶ Significant heterogeneity (I^2 = 65%).
** Data primarily from 1 trial (Carson and colleagues [32]). The findings of a second trial involving 120 patients with hip fractures (Foss and colleagues [47]) reported function results as medians and are not included in the data. However, the findings from this study were similar to those of Carson and colleagues. The results of this outcome at 30 d are similar to 60-d results.

risk for myocardial infarction in the restrictive group than in the liberal group (RR, 0.25 [CI, 0.07 to 0.88]) (50). In contrast, FOCUS found a higher risk for myocardial infarction in the restrictive group than in the liberal group, although this finding was not statistically significant (RR, 1.65 [CI, 0.99 to 2.75]) (32). Combined data from 8 trials (including the TRICC and FOCUS trials) that evaluated risk for myocardial infarction did not find elevated risk (RR, 0.88 [CI, 0.38 to 2.04]); however, the comparison lacked statistical power and the trials could have missed a 2-fold higher risk for myocardial infarction associated with restrictive transfusion. Similar results were found when overall cardiac events were examined.

Three trials involving patients having cardiac surgery compared restrictive transfusion and liberal transfusion, and no difference was found in mortality or cardiac outcomes among these trials (31, 42, 51). Because these patients had undergone revascularization to bypass obstructed coronary arteries, the results may not be applicable to patients with uncorrected underlying coronary artery disease.

Rationale for Recommendations

The panel advised that physicians should consider transfusion when hemoglobin concentration is less than 8 g/dL or when symptoms are present because overall mortality was not adversely affected and use of fewer RBC transfusions reduces cost and risks for adverse effects of transfusion. However, there was some uncertainty about the risk for perioperative myocardial infarction associated with a restrictive transfusion strategy. There was moderate heterogeneity between the results of the 2 major trials, and they were not large enough to precisely define the risks and benefits of transfusion in this setting.

Table 2—Continued

Patients, *n/N*		Effect		Quality	Importance
Restrictive Transfusion Strategy	Liberal Transfusion Strategy	Relative Risk (95% CI)	Absolute Effect		
171/2484 (6.9%)	199/2495 (8.0%)	0.85 (0.7 to 1.03)	Risk reduction, 12 fewer per 1000 (24 fewer to 2 more)	High	Critical
45/1940 (2.3%)	39/1944 (2.0%)	0.88 (0.38 to 2.04)	Risk reduction, 2 fewer per 1000 (12 fewer to 21 more)	Low	Critical
59/1827 (3.2%)	78/1822 (4.3%)	0.72 (0.31 to 1.7)	Risk reduction, 12 fewer per 1000 (30 fewer to 30 more)	Low	Important
20/1380 (1.4%)	25/1380 (1.8%)	0.84 (0.47 to 1.49)	Risk reduction, 3 fewer per 1000 (10 fewer to 9 more)	Moderate	Critical
10/1111 (0.9%)	14/1109 (1.3%)	0.71 (0.32 to 1.59)	Risk reduction, 4 fewer per 1000 (9 fewer to 7 more)	Moderate	Important
180/2149 (8.4%)	223/2157 (10.3%)	0.81 (0.66 to 1)	Risk reduction, 20 fewer per 1000 (35 fewer to 0 more)	Moderate	Important
347/1009 (34.4%)	351/1007 (34.9%)	0.99 (0.88 to 1.11)	Risk reduction, 3 fewer per 1000 (42 fewer to 38 more)	Moderate	Important
2110	2116	–	Mean difference, 0.11 (−0.16 to 0.38)	High	Important

Question 3

In hospitalized, hemodynamically stable patients with the acute coronary syndrome, at what hemoglobin concentration should an RBC transfusion be considered?

Recommendations

The AABB cannot recommend for or against a liberal or restrictive RBC transfusion threshold. Further research is needed to determine the optimal threshold.

Quality of evidence: very low; strength of recommendation: uncertain.

Evidence Summary

The systematic review did not identify any clinical trials evaluating transfusion thresholds in patients with the acute coronary syndrome.

Rationale for Recommendations

Because of a lack of clinical data from randomized, controlled trials, we provide no recommendations about the appropriate hemoglobin transfusion threshold for patients with the acute coronary syndrome. The panel recognized that observational studies in patients with the acute coronary syndrome have been reported (58) but, because of uncontrolled confounding, believed that the evidence from these types of studies was insufficient to support clear recommendations. The panel recommended that 1 or more clinical trials be performed to inform clinicians when patients with the acute coronary syndrome should receive a transfusion.

Question 4

In hospitalized, hemodynamically stable patients, should transfusion be guided by symptoms rather than hemoglobin concentration?

Recommendations

The AABB suggests that transfusion decisions be influenced by symptoms as well as hemoglobin concentration.

Quality of evidence: low; strength of recommendation: weak.

Evidence Summary

Only the FOCUS trial (32) incorporated symptoms into the decision to transfuse. In this trial, patients in the restrictive group received transfusions if hemoglobin concentration was less than 8 g/dL or if they were symptomatic (32). Patients were permitted, but not required, to receive transfusion for symptoms. Overall, transfusions for

symptoms were reported in 15.7% of patients in the restrictive group versus 5.3% in the liberal group. There were no statistically significant differences for any outcome examined.

Rationale for Recommendations

Conventional wisdom, based on physiologic reasoning, indicates that patients with symptoms benefit from RBC transfusion. However, there are limited trial data addressing this issue. In the FOCUS trial, patients in the restrictive group, all of whom could receive transfusions if they were symptomatic, did not have worse outcomes in terms of 30-day mortality or function than those who received transfusions at a hemoglobin threshold of 10 g/dL. Although patients with symptoms were not required to receive transfusions, withholding transfusion would be expected to increase adverse events in the restrictive group. Therefore, the results of this trial support the idea that transfusion should be guided by symptoms for patients with hemoglobin concentrations of 8 g/dL or greater rather than at a higher threshold.

Because transfusion was permitted in the FOCUS trial for patients with hemoglobin concentrations below 8 g/dL, no recommendations can be made about the use of symptoms to guide transfusion below this threshold.

The optimal trial would compare patients receiving transfusions based on hemoglobin concentration with those receiving transfusions only for symptoms. The panel believes that although such a trial would be valuable, it would probably require blinding physicians to the hemoglobin concentration, which raises issues of feasibility. Furthermore, there is probably a lack of clinical equipoise about transfusion in symptomatic patients. Thus, it is unlikely that such a trial will be done.

Discussion

Transfusion of RBCs is a common therapeutic intervention for which variation in clinical practice is considerable. Large observational studies have shown important differences in management of critical care (59–61), orthopedic surgery (13, 59), and cardiovascular surgery (14, 59) patients. On the basis of data from all of the available randomized trials, the panel found little evidence to support a liberal transfusion strategy. The restrictive transfusion thresholds used in the 3 largest randomized, controlled trials were 7 g/dL (50, 52) and 8 g/dL (32). Given these data, the panel recommended (strong recommendation) a restrictive transfusion strategy that uses these thresholds in most patient populations (hemodynamically stable critical care, surgical, and medical). For patients with cardiovascular disease, the panel also suggested (weak recommendation) a restrictive transfusion strategy because 1 large clinical trial (FOCUS) showed a statistically nonsignificant increase in myocardial infarction in the restrictive transfusion group but not an increase in mortality. For patients with the acute coronary syndrome, evidence was not sufficient to make specific recommendations.

If a restrictive transfusion strategy were widely implemented and replaced a liberal strategy, exposure of patients to RBC transfusions would decrease by an average of approximately 40% (RR, 0.61 [CI, 0.52 to 0.72]). This would have a large effect on blood use and the risks for infectious and noninfectious complications of transfusion.

Comparison With Other Guidelines

Previously published guidelines for the use of RBC transfusions, including those from the American Society of Anesthesiologists task force (4), the British Committee for Standards in Haematology (15), and the Australian and New Zealand Society of Blood Transfusion (16), have provided general recommendations for appropriate hemoglobin transfusion thresholds (transfusion is generally not indicated when the hemoglobin concentration is above 10 g/dL but is indicated when it is less than 6 to 7 g/dL). However, none of these guidelines recommended a specific transfusion trigger. Recent guidelines recommended a restrictive strategy (transfusion when the hemoglobin level is less than 7 g/dL) for adult trauma and critical care patients, with the exception of those with acute myocardial ischemia (62). Furthermore, these guidelines recommended avoiding transfusion based only on a hemoglobin trigger. Instead, the decision should be guided by such individual factors as bleeding, cardiopulmonary status, and intravascular volume. In contrast, the European Society of Cardiology has recommended withholding transfusion in patients with the acute coronary syndrome unless the hemoglobin concentration decreases to below 8 g/dL (63).

In contrast to the guidelines discussed, in the current guidelines, we explicitly used an evidence-based process that employed the GRADE method. The addition of new data from recently published clinical trials allowed for specific recommendations about transfusion thresholds. Although individual clinical factors are important, hemoglobin level is one of the critical elements used daily by physicians in the decision to transfuse. Thus, specific evidence-based recommendations on use of hemoglobin levels will help standardize transfusion practice.

Research Recommendations

The strength of the recommendations included in these guidelines is limited by the paucity of clinical trial data in certain patient populations. The results of the 3 largest trials (TRICC [50], TRIPICU [52], and FOCUS [32]) have not been replicated and do not include patients from many other populations who frequently receive transfusions. Clinical trials are needed in other patient populations that include (but are not limited to) patients with the acute coronary syndrome, elderly medical patients recovering from illnesses that result in hospitalization, patients with gastrointestinal bleeding, transfusion-dependent patients, patients with coagulopathy or hemorrhagic shock, and patients with traumatic brain injury. Furthermore, tri-

als are needed to examine lower transfusion thresholds (for example, 6 g/dL), because the current evidence has examined thresholds of 7 g/dL in intensive care unit patients and 8 g/dL in other populations. This relative lack of clinical trial data is a barrier to wider acceptance of these guidelines.

Most of the important potential harms of transfusions are too infrequent to be detected by the evidence that we reviewed, and additional studies and reviews are needed to address this question.

Clinicians make decisions every day with incomplete evidence. We believe these guidelines provide a carefully considered set of recommendations that incorporate the quality of the evidence, benefits and risks of transfusion, and joint judgment of an expert panel from many subspecialties. More definitive recommendations await further clinical trials.

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Note: Guidelines cannot account for individual variation among patients. They are not intended to supplant physician judgment with respect to specific patients or special clinical situations. Accordingly, the AABB considers adherence to these guidelines to be voluntary, with the ultimate determination regarding their application to be made by the physician in the light of each patient's unique circumstances.

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Appendix 2: GRADE Methodology

The GRADE system (39) uses the following 4 ratings for quality of evidence:

"High" indicates considerable confidence in the estimate of effect. The true effect probably lies close to the estimated effect, and future research is unlikely to change the estimate of the health intervention's effect.

"Moderate" indicates confidence that the estimate is close to the truth. Further research is likely to have an important effect on confidence in the estimate and may change the estimate of the health intervention's effect.

"Low" indicates that confidence in the effect is limited. The true effect may differ substantially from the estimate, and further research is likely to have an important effect on confidence in the estimate of the effect and is likely to change the estimate.

"Very low" indicates little confidence in the effect estimate. Any estimate of effect is very uncertain.

The strength of recommendations (for or against intervention) is graded as "strong" (indicating judgment that most well-informed people will make the same choice; "We recommend . . . "), "weak" (indicating judgment that a majority of well-informed people will make the same choice, but a substan-

tial minority will not; "We suggest . . . "), or "uncertain" (indicating that the panel made no specific recommendation for or against interventions; "We cannot recommend . . . "). The panel was instructed that 4 factors should play a role in making a recommendation: quality of evidence, uncertainty about the balance between desirable (benefits) and undesirable effects (harms), uncertainty or variability in values and preferences, and practice setting or uncertainty about whether the intervention represents a wise use of resources (costs).

The GRADE system considers 4 major factors in determination of the strength of recommendations: quality of evidence, balance between desirable (benefits) and undesirable (harms) outcomes, resource use and setting, and patient preferences and values. Although strong recommendations in favor of or against health care intervention typically reflect high-quality evidence, GRADE allows a strong recommendation to be made even if the quality of evidence is not high if other factors support such a recommendation.