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

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

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

EVIDENCE REVIEW Reference librarians conducted a literature search for randomized clinical trials (RCTs) evaluating hemoglobin thresholds for RBC transfusion (1950-May 2016) and RBC storage duration (1948-May 2016) without language restrictions. The results were summarized using the Grading of Recommendations Assessment, Development and Evaluation method. For RBC transfusion thresholds, 31 RCTs included 12,587 participants and compared restrictive thresholds (transfusion not indicated until the hemoglobin level is 7-8 g/dL) with liberal thresholds (transfusion not indicated until the hemoglobin level is 9-10 g/dL). The summary estimates across trials demonstrated that restrictive RBC transfusion thresholds were not associated with higher rates of adverse clinical outcomes, including 30-day mortality, myocardial infarction, cerebrovascular accident, rebleeding, pneumonia, or thromboembolism. For RBC storage duration, 13 RCTs included 5,515 participants randomly allocated to receive fresher blood or standard-issue blood. These RCTs demonstrated that fresher blood did not improve clinical outcomes.

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

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

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ore than 100 million units of blood are collected world-
wide each year, and approximately 13 million red blood

cell (RBC) units are collected in the United States. De-
spite previously published guidelines, there remains substantial
variation in the practice of transfusing patients. Physicians often use
hemoglobin level to decide when to transfuse, although some
guidelines maintain that transfusion should be given for symp-
toms of anemia and not solely based on hemoglobin level.

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

ey will improve the outcomes that are important to patients.

In addition to transfusion reactions and infectious risks associ-
ated with RBC transfusions, it has been suggested that an RBC stor-
age lesion may result in adverse outcomes. Units of RBCs can be
stored up to 42 days. The RBCs stored for longer periods have de-
creased ability to deliver oxygen due to decreased levels of 2,3-
diphosphoglycerate, decreased nitric oxide metabolism, altera-
tions of the RBC membrane leading to increased rigidity, and in-
creased RBC endothelial adherence. In addition, the storage medium
may contain increased levels of free hemoglobin, iron, potas-
sium, and inflammatory mediators that may lead to deleterious
consequences. Furthermore, observational studies suggested that RBCs stored longer than 2 weeks may be associated with increased morbidity and mortality; however, the data were
conflicting. These considerations raise the possibility that trans-
fusion medicine services should preferentially provide fresher RBCs
for transfusion compared with standard issue RBCs.

In 2012, the AABB (formerly known as the American Association
of Blood Banks) published RBC transfusion guidelines based on 19 ran-
domized clinical trials (RCTs) that included 6264 patients. Many
of those RCTs were small (median, 120 patients; range, 22 to 2016 pa-

tients) and had high risk of bias. During the past 4 years, the number
of patients enrolled in RBC transfusion RCTs has more than doubled,
and many studies have incorporated methods to minimize the risk of
bias and enrolled populations of patients receiving frequent blood
transfusions. Therefore, it is timely to reexamine the evidence and pro-
vide updated guidance to the medical community.

Thirteen RCTs have evaluated the effect of RBC storage dura-
tion of transfused RBCs on patient outcomes (7 since 2012). How-
ever, there is currently no formal guidance on the optimal length
of RBC storage prior to transfusion.

Methods

These guidelines provide recommendations for (1) the clinicians car-
ing for hospitalized adult patients who are hemodynamically stable
and candidates for RBC transfusions, and (2) the transfusion medicine ser-

vices responsible for storing and providing RBCs. The AABB commis-
ioned and funded the development of these guidelines through the
AABB clinical transfusion medicine committee. In addition, the board

of directors charged the committee to recruit experts with an interest
in RBC transfusion from other professional organizations.

Guideline Development Process

A committee of experts was assembled. Most of the experts were cur-
rent or former members of the AABB clinical transfusion medicine
committee. There were experts appointed by professional or-

ganizations as subject matter experts (American Association for the
American College of Cardiology: S.V.R.; American Society of Anesthesi-
ologists: A.S.; and American Society of Hematology: T.G.). The com-
mittee also included a patient representative (N.P.). Eight of the phy-
sicians were pathologists or hematologists (most with subspecialty
expertise in transfusion medicine). The other physicians included an
anesthesiologist, cardiologist, internist, critical care medicine physi-

cian, trauma or acute care surgeon, and a Grading of Recommendations
Assessment, Development and Evaluation (GRADE) methodologist (G.G.).

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

Evidence Review and Grading

Systematic Review

The guidelines were developed based on separately published up-
dated systematic reviews of the literature on transfusion thresholds
and RBC storage duration. We performed literature searches of RCTs
evaluating transfusion thresholds from 1950 through May 2016 and
the storage duration of transfused RBCs from 1948 through May
2016. The systematic review included RCTs in which the transfu-
sion groups were assigned on the basis of a clear transfusion trigger
or threshold, which was described as hemoglobin or hematocrit level
that had to be reached before a RBC transfusion was administered.
Trials of patients treated surgically, medically, or both were included
as well as those involving adults or children (but not neonates). For
the RBC storage systematic review, the included RCTs enrolled pa-

tients admitted to the hospital requiring a RBC transfusion and com-
pared fresher vs standard issue RBC transfusions. The term standard
issue used in these guidelines is defined as units selected at any
point within their licensed dating period, but only a small proportion
of RBC units transfused were stored for 36 days to 42 days.

The primary outcome in both systematic reviews was mortality (30-
day mortality for transfusion thresholds and a composite of the longest
follow-up provided in each trial, including 30 days, 90 days, and inh-
ospital mortality for RBC storage duration). Secondary outcomes for
transfusion thresholds included morbidity (eg, nonfatal myocardial
infection, pulmonary edema or congestive heart failure, stroke, throm-
boembolism, renal failure, infection, rebleeding, or mental confusion);
the proportion of patients transfused with allogeneic RBCs, autologous
RBCs, or both; hemoglobin levels (the timing of measurement varied among trials); and the number of RBC units transfused. For RBC storage, the secondary outcomes included adverse events and nosocomial infection. The systematic reviews only included RCTs because observational studies evaluating the effect of transfusion are especially prone to confounding by indication and are likely to yield biased results.45,46

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

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

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Approximate Risk Per-Unit Transfusion of RBCs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Febrile reaction11</td>
<td>1:60*</td>
</tr>
<tr>
<td>Transfusion-associated circulatory overload17,13</td>
<td>1:1000</td>
</tr>
<tr>
<td>Allergic reaction14</td>
<td>1:250</td>
</tr>
<tr>
<td>Transfusion-related acute lung injury15</td>
<td>1:12,000</td>
</tr>
<tr>
<td>Hepatitis C virus infection16</td>
<td>1:1,149,000</td>
</tr>
<tr>
<td>Hepatitis B virus infection17</td>
<td>1:1,208,000 to 1:843,000c</td>
</tr>
<tr>
<td>Human immunodeficiency virus infection16</td>
<td>1:1,467,000</td>
</tr>
<tr>
<td>Fatal hemolysis18</td>
<td>1:1,972,000</td>
</tr>
</tbody>
</table>

$\*$ Estimated to be 1:91 with prestorage leukoreduction and 1:46 with poststorage leukoreduction.

b Indicates the estimated risk per recipient rather than unit.

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

### Good Clinical Practice Statement

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

### Recommendations

#### First Recommendation

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

### Evidence Summary

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

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

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

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

Second Recommendation

The AABB recommends that patients, including neonates, should receive RBC units selected at any point within their licensed dating
### Table 2. Evidence for the Association Between Hemoglobin Transfusion Thresholds and Clinical Outcomes in Hospitalized Adult Patients Who Are Hemodynamically Stable and in Need of a Red Blood Cell Transfusion

<table>
<thead>
<tr>
<th>No. of RCTs</th>
<th>Quality Assessment&lt;sup&gt;a&lt;/sup&gt;</th>
<th>No./Total (%) of Patients by Hemoglobin Transfusion Threshold</th>
<th>Effect</th>
<th>Quality of RCTs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Outcome: 30-d Mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>Restrictive (7-8 g/dL)</td>
<td>470/5221 (9.0)</td>
<td>Liberal (9-10 g/dL)</td>
<td>497/5316 (9.3)</td>
</tr>
<tr>
<td>0.97 (0.81-1.16)</td>
<td>3 fewer deaths per 1000 (15 fewer deaths to 18 more per 1000)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Secondary Outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial Infarction (MI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>Restrictive (7-8 g/dL)</td>
<td>78/4156 (1.9)</td>
<td>Liberal (9-10 g/dL)</td>
<td>69/4147 (1.7)</td>
</tr>
<tr>
<td>1.08 (0.74-1.60)</td>
<td>1 more MI per 1000 (4 fewer MIs to 10 more per 1000)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary Edema (PE) or Congestive Heart Failure (CHF)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Restrictive (7-8 g/dL)</td>
<td>87/3132 (2.8)</td>
<td>Liberal (9-10 g/dL)</td>
<td>114/3125 (3.6)</td>
</tr>
<tr>
<td>0.78 (0.45-1.35)</td>
<td>8 fewer PEs or CHFs per 1000 (13 more PEs or CHFs to 20 fewer per 1000)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke or Cerebrovascular Accident (CA)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Restrictive (7-8 g/dL)</td>
<td>49/3675 (1.3)</td>
<td>Liberal (9-10 g/dL)</td>
<td>62/3668 (1.7)</td>
</tr>
<tr>
<td>0.78 (0.53-1.14)</td>
<td>4 fewer strokes or CAs per 1000 (2 more strokes or CAs to 8 fewer per 1000)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rebleeding</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Restrictive (7-8 g/dL)</td>
<td>215/1489 (14.4)</td>
<td>Liberal (9-10 g/dL)</td>
<td>264/1619 (16.3)</td>
</tr>
<tr>
<td>0.75 (0.51-1.10)</td>
<td>41 fewer events per 1000 (16 more events to 80 fewer per 1000)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>Restrictive (7-8 g/dL)</td>
<td>239/3140 (7.6)</td>
<td>Liberal (9-10 g/dL)</td>
<td>256/3137 (8.2)</td>
</tr>
<tr>
<td>0.94 (0.80-1.11)</td>
<td>5 fewer cases of pneumonia per 1000 (9 more cases to 16 fewer per 1000)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thromboembolism</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Restrictive (7-8 g/dL)</td>
<td>16/2010 (0.8)</td>
<td>Liberal (9-10 g/dL)</td>
<td>21/2009 (1.0)</td>
</tr>
<tr>
<td>0.77 (0.41-1.45)</td>
<td>2 fewer thromboembolisms per 1000 (5 more thromboembolisms to 6 fewer per 1000)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: RCT, randomized clinical trial.

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

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

<sup>c</sup> Could be 1 more death to up to 18 more deaths per 1000 in the restrictive transfusion group.

<sup>d</sup> The blinding of participants and personnel was impossible. The blinding of outcome assessment was inconsistent between trials.

<sup>e</sup> Studies had moderately wide 95% CIs.

<sup>f</sup> I<sup>2</sup> = 58% and P = .04.

<sup>g</sup> Could be 1 more event to up to 16 more events per 1000 in patients in the restrictive transfusion group.
Evidence Summary

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

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

The size of the data markers indicates the weight of the trial; RR, relative risk. Trials published after 2012 have been published since the prior AABB transfusion guidelines.
Figure 2. Association Between Fresher vs Standard-Issue Blood and Mortality in Adults, Neonates, Infants, and Children in Randomized Clinical Trials

<table>
<thead>
<tr>
<th>Source</th>
<th>Fresher Blood</th>
<th>Standard Issue Blood</th>
<th>RR (95% CI)</th>
<th>Favors Fresher Blood</th>
<th>Favors Standard Issue Blood</th>
<th>Weight, %</th>
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</thead>
<tbody>
<tr>
<td>Adults</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>Bennett-Guerrero et al, 2015</td>
<td>11</td>
<td>13</td>
<td>2.12 (0.78-5.75)</td>
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<td>0.1</td>
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<tr>
<td>Aeborn et al, 2012</td>
<td>1</td>
<td>1</td>
<td>2.12 (0.71-6.22)</td>
<td></td>
<td></td>
<td>0.4</td>
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<tr>
<td>Schultmann et al, 2002</td>
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<td>2.12 (0.71-6.22)</td>
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<td>0.4</td>
</tr>
<tr>
<td>Hébert et al, 2005</td>
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<td>1</td>
<td>2.12 (0.71-6.22)</td>
<td></td>
<td></td>
<td>0.6</td>
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<tr>
<td>Steiner et al, 2015</td>
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<td>2.12 (0.71-6.22)</td>
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<td>3.1</td>
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<td>Kor et al, 2012</td>
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<td>Lacroix et al, 2015</td>
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<td>2.12 (0.71-6.22)</td>
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<td>79.2</td>
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<tr>
<td>Subtotal</td>
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<td>20</td>
<td>2.12 (0.71-6.22)</td>
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<td>93.2</td>
</tr>
<tr>
<td>Neoneates, Infants, and Children</td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Dhabangi et al, 2013</td>
<td>1</td>
<td>1</td>
<td>2.12 (0.71-6.22)</td>
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<td>0.1</td>
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<tr>
<td>Strauss et al, 1996</td>
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<td>2.12 (0.71-6.22)</td>
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<td>2.12 (0.71-6.22)</td>
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<td>0.1</td>
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<tr>
<td>Fernandes da Cunha et al, 2005</td>
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<td>2.12 (0.71-6.22)</td>
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<td>2.12 (0.71-6.22)</td>
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<td>1.7</td>
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<tr>
<td>Subtotal</td>
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<td>2.12 (0.71-6.22)</td>
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<tr>
<td>Overall</td>
<td>2179</td>
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<td>2.12 (0.71-6.22)</td>
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<tr>
<td>Subtotal</td>
<td>2179</td>
<td>2179</td>
<td>2.12 (0.71-6.22)</td>
<td></td>
<td></td>
<td>100.00</td>
</tr>
</tbody>
</table>

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

Rationale for Recommendation

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

Discussion

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

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

Limitations

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

Comparison With Other Guidelines

Red blood cell transfusion guidelines from 8 societies during the past 5 years addressed hemoglobin transfusion thresholds. Each of the guidelines recommended a restrictive transfusion strategy with most advising a hemoglobin threshold of 7 g/dL in asymptomatic patients. The updated American Society of Anesthesiology task force guidelines recommended a restrictive hemoglobin transfusion strategy between 6 g/dL and 10 g/dL that was determined by the potential for ongoing bleeding and other clinical variables. In symptomatic patients, these guidelines suggest that
### Table 3. Evidence for the Association Between Red Blood Cell (RBC) Storage Duration and Adverse Patient Outcomes

<table>
<thead>
<tr>
<th>RCTs</th>
<th>Storage Duration of RBCs, No. (Total No.)</th>
<th>Effect</th>
<th>Quality of RCTs</th>
<th>Quality of Evidence</th>
<th>Primary Outcome: 30-d Mortality</th>
<th>Secondary Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Risk of Bias</td>
<td>Inconsistency</td>
<td>Indirectness</td>
<td>Imprecision</td>
<td>Publication Bias</td>
<td>Not</td>
</tr>
<tr>
<td></td>
<td>Fresher</td>
<td>Standard Issue</td>
<td>2032 JAMA November 15, 2016 Volume 316, Number 19</td>
<td></td>
<td></td>
<td>Not</td>
</tr>
<tr>
<td></td>
<td>13</td>
<td>Not detected</td>
<td>3881781 (16.2)</td>
<td>2959185616.4</td>
<td>1.02 (0.93-1.14)</td>
<td>1 more death per 1000</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Not detected</td>
<td>2881781 (16.2)</td>
<td>2959185616.4</td>
<td>1.02 (0.93-1.14)</td>
<td>1 more death per 1000</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Not detected</td>
<td>2881781 (16.2)</td>
<td>2959185616.4</td>
<td>1.02 (0.93-1.14)</td>
<td>1 more death per 1000</td>
</tr>
</tbody>
</table>

#### Note
- Ten studies defined fresher storage duration as 3 days to 10 days; 2 studies defined it as the freshest blood in inventory; and 1 study defined it as less than 20 days.
- Nine studies just used the term standard issue and storage duration was not provided. 3 studies defined it as more than 30 days; 2 studies defined it as 30 days or less.

#### Abbreviation
- RCT: randomized clinical trial

The AABB recommendation for RBC storage is more specific than those from other groups, which were promulgated prior to publication of most of the RCTs that provided evidence for the AABB recommendation. For example, the British Committee for Standards in Haematology and the American College of Critical Care Medicine noted a lack of evidence to recommend fresher compared with standard issue RBCs.[104,105] The Australian and New Zealand Society of Blood Transfusion suggested that fresher RBCs (<5 days old) may be indicated in special situations for children and neonates.[108] The guidelines from the Kidney Disease Improving Global Outcomes Work Group suggest use of fresher RBCs for patients with end-stage renal disease may maximize posttransfusion survival.[102]

#### Research Recommendations
Areas of uncertainty for which RCTs are needed include trials in patient populations outside the intensive care unit that include but are not limited to patients with anemia and thrombocytopenia, patients requiring chronic transfusions and those with coagulopathy, hemorrhagic shock, or both. Furthermore, trials that examine lower hemoglobin transfusion thresholds are needed in patients with acute coronary syndrome and those with cardiovascular disease. A recent meta-analysis of selected trials found a higher risk of acute coronary syndrome but not 30-day mortality among patients with cardiovascular disease who received a restrictive transfusion strategy compared with a liberal transfusion strategy.[109] Although ongoing trials[101,112] evaluating RBC storage duration should be completed, additional trials do not appear warranted at this time.

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

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

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