# Red blood cell transfusion: 2016 clinical practice guidelines from AABB

*Aaron A.R. Tobian,[1] Nancy M. Heddle,[2] Theresa L. Wiegmann,[3] and Jeffrey L. Carson[4]*

Clinical practice guidelines are designed to help clinicians with an educational resource that summarizes the best available medical evidence and the best treatment recommendations.[1] In 2004, the AABB Board of Directors identified development of clinical practice guidelines as a strategic priority to help improve patient care by supporting appropriate transfusion practices and charged the Clinical Transfusion Medicine Committee (CTMC) with preparing these guidelines.[2] The CTMC aims to develop guidelines that physicians can use to ensure proper use of blood components and transfusion service directors can use to develop local transfusion practices that are evidence based.

The Institute of Medicine describes clinical practice guidelines as "statements that include recommendations intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options."[1] Due to the growing importance of guidelines in medical practice, the Institute of Medicine in 2011 developed standards for drafting clinical practice guidelines.[1] The key components include having an explicit development process that is transparent to minimize bias, distortion, and conflicts of interest; involving a multidisciplinary panel; basing the decisions on a rigorous systematic review of the evidence; summarizing the evidence in terms of the risks and benefits for each recommendation; including gaps of knowledge; and providing a rating of the evidence and strength of each recommendation. AABB follows these standards in its generation of transfusion clinical practice guidelines.

To assist in the transparent development of guidelines and grading strength of recommendations, in 2000 a group of individuals formed the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group. This group created the GRADE methodology that assists with the standardization of terms used to describe the quality of data, standardization of terms used to describe strength of recommendations, and a standardized summary presentation of findings and recommendations.[3] The GRADE methodology also promotes explicit description of processes used to conduct the systematic review of literature and generation of recommendations. GRADE also allows for generation of recommendations when consensus is not achieved. The GRADE methodology recommends that a group is formed, the clinical questions are formulated, a systematic review of the literature is performed, and then evidence-based guidelines are developed following the explicit step-by-step methodology of the GRADE system. The GRADE methodology has become the worldwide standard for developing guidelines and AABB has endorsed using GRADE methodology for all guidelines drafted by the association.

AABB has drafted clinical practice guidelines for plasma, platelet (PLT), and RBC transfusion.[4-6] The AABB Board supported publication of these guidelines in journals with a more general medical audience, such as *JAMA* and *Annals of Internal Medicine,* so the guidelines can have broader impact on the individuals who are most often ordering transfusions. Overall, AABB's guidelines have been well received. The original RBC transfusion guideline[4] has been cited more than 500 times in less than 4 years and the PLT transfusion guideline[5] was the number one manuscript downloaded from the *Annals of Internal Medicine* journal website in 2015 (>60,000 times). In addition, a recent study performed completely independent of AABB (and not including any former or current guideline panel members) evaluated the methodologic quality and rigor of development of RBC transfusion guidelines from 13 organizations using the AGREE II instrument (Appraisal of

**ABBREVIATION:** CTMC = Clinical Transfusion Medicine Committee.

From the [1]Department of Pathology, Johns Hopkins University, Baltimore, Maryland; the [2]Department of Medicine, McMaster University, Hamilton, Ontario, Canada; the [3]AABB, Bethesda, Maryland; and the [4]Division of General Internal Medicine, Rutgers Robert Wood Johnson Medical School, New Brunswick, New Jersey.

*Address reprint requests to*: Aaron Tobian, MD, PhD, Transfusion Medicine Division, Department of Pathology, Johns Hopkins Medical Institutions, 600 N. Wolfe Street, Carnegie 437, Baltimore, MD 21287; e-mail: atobian1@jhmi.edu.

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Guidelines, Research and Evaluation) and found that AABB's guideline was the highest quality.[7]

The Institute of Medicine recommends that following publication of clinical practice guidelines the society/group developing the guidelines should continue to monitor the medical evidence and update the guidelines when new data would lead to a change in the recommendations.[1] Since AABB's RBC guideline was originally published in 2012,[8] there have been 15 new randomized trials of more than 6000 patients enrolled to evaluate the best transfusion threshold[9]; this clinical trial database is double the number of carefully studied transfused patients available from the previous guidelines. These new data include several prominent trials that evaluated patients with gastrointestinal hemorrhage and cardiac surgery.[10-12] In addition, no previous clinical practice guidelines have addressed how RBC storage duration impacts morbidity or mortality. This question has been evaluated in eight randomized trials since 2012,[13] including two large trials ABLE and RECESS,[14,15] the TOTAL trial in children,[16] and the ARIPI trial, which is the only study performed in neonates.[17] Thus, AABB believed that the new data would permit updated guidelines to address both RBC storage duration and transfusion thresholds, with the anticipation that these recommendations would incorporate broader patient populations, include more precise hemoglobin (Hb) thresholds, and provide recommendations based on stronger evidence than the original guidelines. Consequently, in 2015 the AABB Board charged the CTMC with updating the RBC transfusion guideline.

AABB clearly recognizes that the clinical practice guidelines are suggestions for care and not inflexible rules. Advancing high-quality care for individual patients is a priority to the association. To emphasize this issue, the updated RBC guideline includes a good clinical practice statement in both the abstract and the text of the document. "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. Such variables should include the rate of hemoglobin decline, intravascular volume status, shortness of breath, exercise tolerance, lightheadedness, chest pain thought to be cardiac in origin, hypotension or tachycardia unresponsive to fluid challenge, and patient preferences."[8]

The updated RBC transfusion guideline is composed of two primary recommendations.[8]

**Recommendation 1: AABB recommends a restrictive RBC transfusion threshold of 7 g/dL in hospitalized hemodynamically stable adult patients, including critical care patients, rather than 10 g/dL (strong recommendation, moderate quality evidence). For patients undergoing orthopedic surgery and cardiac surgery and those with existing cardiovascular disease, AABB recommends a restrictive RBC transfusion threshold of 8 g/dL (strong recommendation, moderate quality evidence). The restrictive transfusion threshold of 7 g/dL is likely comparable to 8 g/dL, but randomized trial evidence is not available for all patient categories. These recommendations apply to all but the following conditions, where the evidence is judged to be insufficient for any recommendation: acute coronary syndrome, severe thrombocytopenia in hematology/oncology patients at risk of bleeding, and chronic transfusion-dependent anemia.**[8]

While screening of transfusion-transmissible infections has dramatically increased the safety profile of RBC transfusion, there is still a risk of adverse events such as transfusion-related acute lung injury, transfusion-associated circulatory overload, or a febrile reaction. If there is no substantial benefit to the RBC transfusion, the recipient is exposed only to the potential risks of the transfusion. Thus, it is best to minimize transfusions if possible.

More than 12,000 patients with a wide spectrum of diseases have participated in 31 randomized trials evaluating transfusion thresholds.[9] The restrictive arms of these trials had a transfusion threshold of 7 to 8 g/dL and the liberal arms had a transfusion threshold of 9 to 10 g/dL. The systematic review and meta-analysis found no evidence that individuals in the restrictive arm of these trials were at any greater risk of morbidity or mortality.[9] There were no significant differences in the findings of the trials that used a restrictive transfusion threshold of 7 g/dL compared to a restrictive transfusion threshold of 8 g/dL and the panel suspects a restrictive transfusion threshold of 7 g/dL for all patients may be safe. However, this lower threshold has not been formally tested and there may be issues for the recovery of patients immediately undergoing physical exertion (e.g., orthopedic surgery patients) or increased rates of myocardial infarction in patients with preexisting cardiovascular disease. Consequently, AABB recommends different restrictive transfusion thresholds for various patient populations.

**Recommendation 2: AABB recommends that 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).**[8]

Over the past 10 years, there has been substantial investigation into the RBC "storage lesion." Observational studies suggested RBCs stored for longer periods of time were associated with increased morbidity and mortality.[18,19] However, 13 randomized trials, which enrolled more than 5000 patients, showed no evidence that fresh RBCs reduced mortality compared to standard issue RBCs.[8,13] In addition, individuals who received standard issue RBCs were at no higher risk for adverse events and

actually at a lower risk of nosocomial infections compared to those who received fresh RBCs.[13] The difference in nosocomial infection could be due to blood processing methods.[20] Overall, AABB recommends that standard issue RBCs be transfused on a routine basis.[8]

## AREAS FOR FUTURE RESEARCH

The questions concerning RBC storage duration have been thoroughly investigated in very-low-birthweight infants/neonates, children, and adults.[8,13] The results of these randomized trials have been consistent showing no increased risk associated with transfusion of standard issue RBC units; however, the question of whether very old (36 to 42 days of storage) compared to very fresh (storage duration of less than 7 days) has not been addressed by any of these trials.[21] There are currently a number of large trials that are or will soon be completed allowing for a meta-analysis with data from more than 40,000 patients.[22,23] Further trials in this area may not be warranted.

There are also a number of questions remaining dealing with transfusion thresholds for certain patient populations. AABB was unable to make a recommendation for the following three patient groups: acute coronary syndrome, severe thrombocytopenia in hematology/oncology patients at risk of bleeding, and chronic transfusion-dependent anemia. In contrast to almost all other patient groups, two trials enrolling a total of 155 patients with acute coronary syndrome found a trend toward increased mortality among individuals randomized to the restrictive transfusion approach.[24,25] These findings were consistent with the trial's prespecified a priori hypotheses,[24,25] an observational study of patients with underlying cardiovascular disease,[26] and animal models.[27,28] However, small trials can be unreliable. Thus, AABB recommends further research in this area and did not make a recommendation for a restrictive or liberal transfusion approach.[8]

In addition to patients with acute coronary syndrome, AABB did not make recommendations for patients with severe thrombocytopenia or patients who are chronically dependent on transfusion support. Patients with severe thrombocytopenia are at higher risk of bleeding and anemia may increase their measured bleeding time.[29,30] These patients may benefit from RBC transfusion to increase PLT responsiveness.[31,32] Two small pilot trials have shown these patients may be treated with a restrictive transfusion approach,[33,34] but further research is needed. In addition, there are very little data available on transfusion thresholds for patients with chronic transfusion-dependent anemia. Finally, it is unknown if 7 g/dL is the best transfusion threshold or rather a lower Hb threshold could also provide sufficient oxygenation without additional RBC transfusions.

AABB through its clinical practice guideline initiative has made important contributions to improving the clinical practice of transfusion medicine. While the quality and number of clinical trials have increased substantially over recent years, much work remains to fully inform clinical practice. As new evidence emerges, it is essential that AABB guidelines are updated and made available to clinicians through the medical literature.

### CONFLICT OF INTEREST

JLC is the principal investigator on a pending grant proposal to assess transfusion thresholds for patients with an acute myocardial infarction. All other authors have disclosed no conflicts of interest.

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