AABB Red Blood Cell Transfusion Guidelines

Something for Almost Everyone

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In this issue of JAMA, Carson and colleagues\(^1\) provide an important update to the red blood cell (RBC) transfusion guidelines developed in 2012 by the AABB (formerly the American Association of Blood Banks).

The authors based the current guidelines and recommendations on the results of 31 randomized clinical trials (RCTs) performed in a variety of different clinical settings involving more than 12,500 patients who were randomized to receive transfusion triggered by either a hemoglobin concentration of less than 7 g/dL to 8 g/dL (restrictive strategy referred to as the conservative strategy) or a hemoglobin concentration of less than 9 g/dL to 10 g/dL (liberal strategy). The evaluation used the Grading of Recommendations Assessment, Development, and Evaluation methods and appropriately considered only RCTs, thereby avoiding the invariable confounding present in observational studies examining blood transfusion. In aggregate, the analysis convincingly demonstrated that adverse consequences (mortality and major morbidity) were not more common among patients assigned to a conservative transfusion strategy compared with a liberal one. Thus, the authors of this guideline recommend a conservative transfusion policy.

Unlike the previous 2012 version of the RBC transfusion guidelines that recommended overlapping hemoglobin concentration triggers of 7 g/dL to 8 g/dL for most inpatients,\(^2\) these updated guidelines recommend 2 distinct tiers of hemoglobin triggers for RBC transfusions: hemoglobin concentration of less than 7 g/dL for stable, adult inpatients including those in the intensive care unit, and hemoglobin concentration of less than 8 g/dL for a select group of postsurgery patients or those with preexisting cardiac disease. The 2-tiered approach acknowledges the current state of the evidence and also provides support for making more individualized transfusion decisions.

In the intensive care unit setting, transfusions are given to reduce the risk of major morbidity and mortality, and such outcomes can be achieved using either a conservative hemoglobin concentration transfusion trigger of less than 7 g/dL or a liberal transfusion strategy. However, for some patients, such as those undergoing hip replacement surgery, functional recovery has traditionally represented the primary rationale for transfusion, and this outcome can also be achieved using either a conservative hemoglobin concentration transfusion trigger of less than 8 g/dL or a liberal strategy. Thus, although both critically ill patients and patients who had major orthopedic surgery were safely managed with a conservative transfusion strategy, the study design tested a hemoglobin concentration transfusion trigger of 7 g/dL for critically ill patients and a hemoglobin transfusion trigger of 8 g/dL for patients undergoing orthopedic surgery, with different primary outcomes. Thus, there is no definitive evidence of the safety of using a hemoglobin transfusion trigger of 7 g/dL in some specific patient populations (ie, those undergoing orthopedic surgery and cardiac surgery); hence, the guidelines offer 2 RBC transfusion thresholds.

Whether patients undergoing cardiac surgery or older patients (>65 years) undergoing major orthopedic surgery can be safely managed at a hemoglobin transfusion trigger of 7 g/dL is not known. In an RCT of 2007 patients undergoing cardiac surgery who were randomized to receive transfusion at a hemoglobin level of less than 7.5 g/dL compared with less than 9 g/dL, there was no difference in the primary composite outcome of serious morbidity events. However, in a predefined secondary analysis, 90-day mortality was higher in the group assigned to the conservative trigger (4.2%) compared with the liberal trigger (2.6%) (hazard ratio, 1.67 [95% CI, 1.00-2.67]; \(P = .045\)). Similarly, in a study of 2016 patients who underwent surgical hip repair, no difference was observed in the primary composite end point of mortality or functional recovery among those randomized to transfusion for a hemoglobin level of less than 8 g/dL vs less than 10 g/dL. However, in a predefined secondary analysis, acute myocardial infarction was observed more commonly in those assigned to the conservative trigger (3.8%) compared with the liberal trigger (2.3%) (odds ratio, 0.76 [95% CI, 0.30-1.91]). These secondary analyses do not provide sufficient data for drawing definitive conclusions, but the observations among patients assigned to the restrictive intervention groups suggest that a hemoglobin transfusion trigger of less than 7 g/dL may not be safe for all patients. More will be learned following the completion of a trial\(^3\) currently testing a hemoglobin trigger of less than 7 g/dL for patients undergoing cardiac surgery.

The AABB’s current 2-tier recommendation for RBC transfusion specifically excludes certain patient populations such as those with acute coronary syndromes. Even though the Grading of Recommendations Assessment, Development, and Evaluation methods did not permit a specific guideline recommendation for these patients based on the current evidence, these patients still need to be managed when they present to the hospital. Two small pilot RCTs,\(^4,5\) the Myocardial Ischemia and Transfusion and the Conservative vs Liberal Red Cell Transfusion in Acute Myocardial Infarction, evaluated conservative (at hemoglobin level of 8 g/dL) vs liberal (at hemoglobin level of 10 g/dL) transfusion thresholds in a total of 155 patients who were experiencing acute cardiac events. An unexpected large effect was observed with better survival among patients assigned to a liberal vs conservative transfu-
sion strategy (1.8% mortality vs 13.0% mortality, respectively). These preliminary data need to be confirmed in a properly powered RCT and serve as an important reminder that a conservative RBC transfusion strategy may not be safe for all patients. While awaiting confirmation of the results of these pilot studies, it seems prudent to consider a liberal approach to transfusion for patients with acute coronary syndromes.

Good clinical practice dictates that the decision to transfuse should not be solely based on the hemoglobin level. Clinical factors, availability of alternative therapies, and patient preferences should be considered. That does not mean that guidelines provided by Carson and colleagues are without value, but rather that guidelines reflect general recommendations that apply to most patients in most situations. A major limitation of these guidelines is that they are based on hemoglobin level as the transfusion trigger. Hemoglobin is a measure of the oxygen carrying capacity of blood, but does not indicate tissue oxygen delivery or the level of tissue oxygenation. Perhaps direct measurement of tissue oxygenation using noninvasive methods or plasma markers, such as base deficit, lactate, or other biomarkers, coupled with the measurement of hemoglobin level will provide a more clinically relevant indication of the need for RBC transfusion. Hopefully, future RBC transfusion guidelines will be able to incorporate rigorous evidence from more physiological markers that assess tissue oxygenation.

The promulgation of conservative RBC transfusion guidelines raises the following questions: How low can the transfusion threshold go? Should withholding transfusion to even lower hemoglobin values (eg, <6 g/dL) be studied? There would likely be diminishing returns in doing so and that the risks of serious morbidity and mortality at that hemoglobin threshold will likely outweigh the risks of transfusion. The current body of RCTs that served to inform these guidelines indicates that patients in the liberal transfusion intervention groups did not experience higher rates of morbidity or mortality compared with those in the restrictive transfusion groups, despite receiving many more RBC units. Thus, prior observational reports of serious adverse outcomes associated with RBC transfusion have not been borne out by the RCT data. It may follow that the risks of transfusing a unit of RBCs is lower than previously thought and would not justify accepting excessive risks at very low hemoglobin values. Along this line, even though the safety of the hemoglobin transfusion trigger of less than 7 g/dL has been amply demonstrated in patients in intensive care units, this transfusion trigger should not be extended to any other patient population unless its safety has been demonstrated in properly conducted studies.

This updated version of the AABB guidelines also includes for the first time a recommendation of how long RBC units should be stored before transfusion. Among 13 evaluated RCTs that collectively enrolled 5515 patients, no clinical differences (including 30-day mortality, myocardial infarction, cerebrovascular accident, rebleeding, pneumonia, or thromboembolism) were found among those assigned to receive longer-storage RBCs compared with RBC units with shorter-storage duration. Thus, the AABB did not recommend making any changes in the usual blood bank practice of issuing the oldest RBCs first.

This recommendation reveals science as it should evolve; the hypothesis that the receipt of standard issue RBC units could lead to higher morbidity and mortality was suggested by an observational study of patients undergoing cardiac surgery. When this concept was tested in well-designed RCTs, the original hypothesis was shown not to be valid in patients undergoing cardiac surgery, critically ill patients, or premature neonatal patients. Rather than the duration of storage, the indication for RBC transfusion remains the more pertinent clinical question.

These new guidelines from the AABB represent medicine at its best in that they are evidence based, derived from RCTs, reflect important clinical perspectives, and are definitive for conditions in which data are substantial, but provide greater flexibility for conditions in which data are less certain.

ARTICLE INFORMATION

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REFERENCES


