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UPDATES IN RED BLOOD CELL TRANSFUSION THRESHOLDS

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AABB RED BLOOD CELL TRANSFUSION INTERNATIONAL GUIDELINES

Randomized controlled trials (RCTs) assessing outcomes of different transfusion thresholds typically compare higher hemoglobin thresholds (liberal transfusion strategy) with lower ones (restrictive transfusion strategy) for red blood cell (RBC) transfusions.¹ The numbers of these trials continue to increase.¹ The first guidelines from the Association for the Advancement of Blood & Biotherapies (AABB), issued in 2012, included 19 RCTs. The updated guidelines from 2016 included 31 RCTs.^{2,3} In 2018, the Transfusion and Anemia Expertise Initiative published guidelines based on five RCTs for RBC transfusion in critically ill children.⁴ In 2021, an updated Cochrane systematic review included 48 trials.⁵ Given the expanded evidence base and the prior absence of AABB guidelines specific to children, the AABB Clinical Transfusion Medicine Committee reexamined the transfusion threshold evidence and provided updated guidance.¹

AABB commissioned and funded updated guidelines through the AABB Clinical Transfusion Medicine Committee. These guidelines follow existing standards of trustworthiness,⁶ including using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach for summarizing evidence and moving from evidence to recommendations.⁷ The international panel included members with expertise in transfusion medicine, supported by a GRADE methodologist and a patient partner.¹

As part of this study, researchers reviewed evidence from 45 RCTs with 20,599 adults, five RCTs identified within the Transfusion and Anemia Expertise Initiative in 2018, and two additional pediatric trials (2,730 participants).⁸⁻¹⁰ The systematic reviews included RCTs in which the transfusion groups were assigned based on a clear transfusion threshold, described as the hemoglobin concentration or hematocrit level required before RBC transfusion. Outcomes in adults included 30-day mortality, nonfatal myocardial infarction, pulmonary edema or congestive heart failure, stroke, thromboembolism, acute kidney injury, infection, hemorrhage, mental confusion, the proportion of patients with an allogeneic or autologous RBC transfusion, hemoglobin concentration (postoperative or discharge), number of RBC units transfused and quality of life.¹

RECOMMENDATIONS FOR ADULTS

RECOMMENDATION 1

For hospitalized adult patients who are hemodynamically stable, the international panel recommends a restrictive RBC transfusion strategy in which transfusion is considered when the hemoglobin concentration is less than 7 g/dL (strong recommendation, moderate certainty evidence). In accordance with the restrictive strategy threshold used in most of the trials for subgroups of patients, clinicians may choose a threshold of 7.5 g/dL for patients undergoing cardiac surgery and 8 g/dL for patients undergoing orthopedic surgery or those with preexisting cardiovascular disease.¹

RECOMMENDATION 2

For hospitalized adult patients, the panel suggests a restrictive RBC transfusion strategy in which transfusion is considered when the hemoglobin concentration is less than 7 g/dL in those with hematologic and oncologic disorders (conditional recommendation, low certainty evidence).¹

Thirty trials, which comprised data from 16,092 participants, evaluated 30-day mortality, with a pooled relative risk of 1.00 (95% CI, 0.86-1.16). The results showed that the restrictive strategy resulted in a 32.4% absolute reduction (95% CI, 37.3%-27.5% fewer deaths) in those receiving a transfusion.¹

There were no apparent differences between transfusion strategies for morbidity outcomes. Data from three RCTs that enrolled 448 participants suggested the risk of bleeding in hematology and oncology patients was uninfluenced by transfusion strategy (relative risk, 1.03; 95% CI, 0.87 to 1.23; absolute difference, 0.6%; 2.7% fewer to 4.8% more bleeding events).¹

The most common restrictive transfusion strategy applied in the trials was 7 or 8 g/dL, although variations included critical care and cardiac surgery trials that used a transfusion strategy of 7 to 7.5 g/dL and orthopedic and acute myocardial infarction trials that used a restrictive strategy of 8 g/dL.¹

In hematology and oncology inpatients, the panel suggests transfusion at 7 g/dL (conditional, low certainty evidence). However, the number of patients enrolled in these trials is smaller than that in many other clinical subgroups because new RCTs have suggested neither harm nor increased bleeding when using a restrictive threshold. There were insufficient trial data to inform recommendations in outpatient transfusion management.¹

RECOMMENDATIONS FOR CHILDREN

RECOMMENDATION 3

For critically ill children and hospitalized children at risk of critical illness who are hemodynamically stable and without a transfusion-dependent hemoglobinopathy, cyanotic cardiac condition or severe hypoxemia, the international panel recommends a restrictive transfusion strategy in which a

transfusion is considered when the hemoglobin level is less than 7 g/dL compared with one of less than 9.5 g/dL (strong recommendation, moderate certainty evidence).¹

RECOMMENDATION 4

The international panel suggests considering a transfusion threshold for hemodynamically stable children with congenital heart disease that is based on the cardiac abnormality and stage of surgical repair: 7 g/dL (biventricular repair), 9 g/dL (single-ventricle palliation), or 7 to 9 g/dL (uncorrected congenital heart disease) (conditional recommendation, low certainty evidence).¹

The largest single intensive care unit RCT reported a 51.8% absolute reduction in transfusions in the restrictive strategy group compared with the liberal strategy group,¹¹ with no significant difference reported for 30-day mortality within a meta-analysis of five RCTs (relative risk, 0.44; 95% CI, 0.04-4.45). There were no clear differences in the morbidity outcomes.¹

Optimal transfusion practice should rely not only on hemoglobin concentration thresholds, but also on incorporating patients' symptoms, signs, comorbid conditions, rate of bleeding, values and preferences. This guidance is particularly important because clinicians commonly use only hemoglobin concentration to decide when to transfuse.¹² Blood management programs that audit blood should attend to these broader considerations in their policies and decisions.

While a specific recommendation on the shelf-life of RBCs provided in 2016² was removed as a recommendation, it was stated that given the RCTs demonstrated no effect on mortality,^{13,14} the storage age of transfused RBCs need not be considered in transfusion decisions. This and other guidelines published after 2016 recommend restrictive transfusion strategies.¹

The panel recommends restrictive transfusion strategies, typically with a threshold of 7 g/dL for both adult and pediatric patients. The panel recognizes important considerations that will differ between patients, including signs, symptoms, comorbid conditions, and patient values and preferences. The recommendation is strong, based on moderate certainty evidence from most patients, but conditional, based on lower certainty evidence subgroups that include hematologic and oncologic disorders in adults and cyanotic cardiac conditions in infants.¹

TRANSFUSION STRATEGIES IN MYOCARDIAL INFARCTION AND ANEMIA

The primary objective of the Myocardial Ischemia and Transfusion (MINT) trial was to determine whether the risk of mortality or myocardial infarction through 30 days differed between a restrictive transfusion strategy (hemoglobin threshold, 7 to 8 g/dL) and a liberal transfusion strategy (hemoglobin threshold, <10 g/dL) among patients with acute myocardial infarction and anemia.¹⁵

This open-label, randomized trial was conducted at 144 sites in the Australia, Brazil, Canada, France, New Zealand and the United States. The trial rationale and design have been reported previously.¹⁶ The study enrolled adults (≥ 18 years of age) with ST-segment elevation or non-ST-segment elevation myocardial infarction, defined in accordance with the Third Universal Definition of Myocardial Infarction,¹⁷ along with anemia (hemoglobin level, <10 g/dL within 24 hours before randomization).¹⁸

In the restrictive-strategy group, transfusion was permitted but not required when the hemoglobin level was less than 8 g/dL, and was strongly recommended when the level was less than 7 g/dL or when anginal symptoms were not controlled with medications. In the liberal-strategy group, one unit of RBCs was administered after randomization, and RBCs were transfused to maintain the hemoglobin level at or above 10 g/dL until the time of hospital discharge or 30 days.¹⁸

The primary outcome was a composite of myocardial infarction or mortality from any cause up to 30 days after randomization. The prespecified secondary outcomes were the individual components of the primary outcome (myocardial infarction or mortality at 30 days) and the composite outcome of mortality, myocardial infarction, ischemia-driven unscheduled coronary revascularization or readmission to the hospital for an ischemic cardiac condition within 30 days.¹⁸

A total of 3,506 patients were enrolled from April 2017 through April 2023, and 3,504 were included in the analyses after two patients did not approve the use of their data. The mean age of the patients was 72.1 years, and 45.5% of the patients were women. Follow-up at 30 days was complete for 3,447 patients (98.3%) who had undergone randomization.

The mean hemoglobin level was lower in the restrictive-strategy group than in the liberal-strategy group by 1.3 g/dL (95% confidence interval [CI], 1.2 to 1.4) on day 1 and lower by 1.6 g/dL (95% CI, 1.5 to 1.7) on day 3. The total number of units of RBCs transfused in the liberal-strategy group was 3.5 times the number transfused in the restrictive-strategy group (4,325 units vs. 1,237 units). The mean (\pm SD) number of RBC transfused in the liberal-strategy group was 2.5 ± 2.3 , compared with 0.7 ± 1.6 in the restrictive-strategy group. The median duration of hospitalization from randomization until discharge, withdrawal, or death was 5 days (interquartile range, 2 to 10) in the two groups.

Myocardial infarction or mortality from any cause at 30 days (the primary outcome) occurred in 295 of 1,749 patients (16.9%) in the restrictive-strategy group and 255 of 1,755 patients (14.5%) in the liberal strategy group. The crude risk ratio (restrictive vs. liberal) was 1.16 (95% CI, 1.00 to 1.35). At 30 days, mortality had occurred in 173 of 1,749 patients (9.9%) in the restrictive-strategy group and 146 of 1,755 patients (8.3%) in the liberal strategy group (risk ratio, 1.19; 95% CI, 0.96 to 1.47), and myocardial infarction had occurred in 8.5% and 7.2% of the patients, respectively (risk ratio, 1.19; 95% CI, 0.94 to 1.49). Mortality, myocardial infarction, ischemia-driven unscheduled coronary revascularization or readmission to the hospital for an ischemic cardiac condition within 30 days occurred in 19.6% of the patients in the restrictive-strategy group, and 17.4% of those in the liberal-strategy group (risk ratio, 1.13; 95% CI, 0.98 to 1.29). Cardiac-related mortality was more common in the restrictive-strategy group than in the liberal-strategy group (5.5% and 3.2%, respectively; risk ratio, 1.74; 95% CI, 1.26 to 2.40); the risk of other clinical-outcome events did not differ significantly between the two groups.

In the MINT trial, the study did not find a significant difference in the incidence of recurrent myocardial infarction or mortality at 30 days between patients with acute myocardial infarction and anemia who were assigned to a restrictive transfusion strategy and those who were assigned to a liberal transfusion strategy. However, the liberal transfusion strategy was consistently favored in point estimates for the primary outcome and mortality, cardiac-related mortality, recurrent myocardial

infarction, and the composite of mortality, myocardial infarction, ischemia-driven unscheduled coronary revascularization or readmission to the hospital for an ischemic cardiac condition.¹⁸

Whether or not to transfuse is an everyday decision faced by clinicians caring for patients with acute myocardial infarction. The researchers observed that the 95% confidence interval contains values that suggest a clinical benefit for the liberal transfusion strategy and does not include values that suggest a benefit for the more restrictive transfusion strategy.¹⁸

The results show that in patients with acute myocardial infarction and anemia, a liberal transfusion strategy did not significantly reduce the risk of recurrent myocardial infarction or mortality at 30 days. Trial endpoints suggest some benefit of a liberal strategy over a restrictive strategy, but additional studies would be needed to confirm that conclusion.¹⁸

The addition of both the AABB recommendations and the MINT trial is a good opportunity for leaders of patient blood management programs to review their current RBC threshold procedures. They can be presented to the transfusion committees using the evidence provided as support to guide clinical practice decisions.

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