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

By Richard Gammon MD, Medical Director at OneBlood Inc., Orlando, Florida.

Background

In 2015, 11 million red blood cell (RBC) units were transfused in the U.S.[1] Clinicians who ordered these (and other) transfusions demonstrated substantial variation in their decision-making processes, with a primary reason being current limitations to the quality of evidence applying to transfusion-related benefits and harms. The benefits vary with the clinical situation, while the risks are numerous, including at least 50,000 transfusion reactions per year, with a handful leading to death. The cost is considerable as well—a minimum of $2.5 billion for products alone, which can be multiplied three-to-five-fold if one also incorporates the handling and administration costs.[2] Despite longstanding, widespread use of RBC transfusions, the product administration indications remain controversial.[3]

Three Categories of Risk/Adverse Effects from Blood Transfusion

Clinical Event	Risk/Unit	
Allergic/Urticaria	1 in 100	Common
RBC Alloimmunization	1 in 100	Common
TACO	1 in 100	Common
TRALI	1 in 5,000	Not so rare
Hemolytic Rxn	1 in 6,000	Not so rare
Wrong Unit Given	1 in 15,000	Not so rare
Hepatitis B	1 in 1,200,000	Rare
Hepatitis C	1 in 2,000,000	Rare
HIV 1 and HIV 2	1 in 2,000,000	Rare

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Guideline Development Process

AABB commissioned and funded the development of these guidelines through its Clinical Transfusion Medicine Committee. The committee was charged with recruiting subject matter experts having an interest in RBC transfusion, including individuals representing other professional organizations. These entities included the American Association for the Surgery of Trauma, the American College of Cardiology, the American Society of Anesthesiologists, the American Society of Hematology, and the Society of Critical Care Medicine. Most of these experts were current or former members of the AABB's

Key Points

- Recommendation 1
  » RBC transfusion not indicated until hemoglobin falls to 7 g/dL in hospitalized hemodynamically stable adult patients.
  » For orthopedic and cardiac surgery patients, and those with preexisting cardiovascular disease, a restrictive RBC transfusion threshold with a hemoglobin of </= 8 g/dL is recommended.

- Recommendation 2
  » Patients, including (in many cases) 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.

Clinical Transfusion Medicine Committee. The committee also featured a patient representative and a Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodologist.

The authors performed a literature search for randomized clinical trials (RCTs) evaluating hemoglobin thresholds for RBC transfusions (1950-through-May 2016). Results were summarized using the GRADE method.[3] The study reviewed 31 RCTs and involved a total of 12,587 participants. Results for patients transfused at restrictive thresholds (defined as transfusion not indicated until the hemoglobin level was 7-8 g/dL) were compared to those for patients transfused at liberal thresholds (transfusion not indicated until the hemoglobin level was 9-10 g/dL). For the RBC storage systematic review, the authors included RCTs that enrolled patients admitted to the hospital who required at least one RBC transfusion and compared fresher vs. standard-issue RBC transfusions.[4] The term "standard issue" used in these guidelines was defined as units selected at any point within their licensed dating period.

Outcomes

The primary outcome was mortality – i.e., 30-day mortality for the "transfusion thresholds" portion of this study and "a composite of the longest follow-up provided in each trial, including 30 days, 90 days, and in-hospital mortality" for the "RBC storage duration" portion.

Secondary outcomes for transfusion thresholds included morbidity (i.e., nonfatal myocardial infarction, pulmonary edema or congestive heart failure, stroke, thromboembolism, renal failure, infection, re-bleeding, or mental

confusion). For RBC storage, secondary outcomes included adverse events and nosocomial infection. Systematic reviews included only RCTs because observational studies evaluating the transfusion effects were especially prone to confounding by indication and likely to yield biased results.[5,6]

Evidence profiles were prepared that displayed data in terms of benefits and harms for the most important outcomes. These profiles were the basis for decisions regarding the rating of quality, for risk of bias, lack of consistency, lack of directness, lack of precision, and possible publication bias. Overall, the quality of evidence for each outcome was assessed for the systematic reviews of: (1) transfusion thresholds, and (2) impact of RBC storage durations. The committee then developed its final quality ratings and determined the strength of the recommendations accordingly.[3]

Recommendation 1: AABB (see Guideline Development Process above) recommended a restrictive RBC transfusion threshold in which the transfusion was not indicated until the hemoglobin level was 7 g/dL for hospitalized adult patients who were hemodynamically stable, including critically ill patients. For patients undergoing orthopedic or cardiac surgery and those with preexisting cardiovascular disease, AABB recommended a restrictive RBC transfusion threshold (hemoglobin level of 8 g/dL). Both were strong recommendations based on moderate quality evidence. Any recommendation for patients with acute coronary syndrome, severe thrombocytopenia, and chronic transfusion-dependent anemia lacked sufficient evidence.[3]

Evidence Summary: In the restrictive transfusion group, the absolute difference in 30-day mortality was three fewer deaths per 1,000 patients (95% CI, 15 fewer deaths to 18 more deaths per 1000 in the liberal group). There was no evidence to suggest patients were harmed by restrictive transfusion protocols. Liberal transfusion was not found to be associated with an increased risk of infection as had been found in a prior meta-analysis.[7] There were no differences in the other assessed outcomes, including ability to walk, multiple measures of function, fatigue, and length of hospital stay.[3] The 30-day mortality relative risks (RR) were similar with no evidence that these two threshold groups were statistically different (RR = 0.97 (0.81-1.16), P = 0.56).[3]

Recommendation 2: AABB recommended 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. This was a strong recommendation using moderate quality evidence.

Evidence Summary: There were 13 trials meeting the inclusion criteria, some of which included children, neonates, and infants with very low birth weights. Most patients had an acute critical illness or surgical hemorrhage. The storage duration of the standard-issue blood varied between trials.

For the two primary trials involving neonates, the mean storage durations at the time of transfusion were 1.6 days and 5.1 days for fresher RBCs vs. 9.0 days and 14.1 days for standard issue RBCs.[8,9] Trials of adults ranged from a median of 4 days (mean, 12.1 days) for fresher RBCs vs. a median of 19 days (mean, 28 days) for standard issue RBCs.[3] In both neonates and adults there was no evidence that transfusion of fresher RBCs was superior to standard issue RBCs for the outcome of mortality (RR, 1.04; 95% CI, 0.95-1.14). It should be noted that the RBC storage duration trials did not evaluate patients undergoing massive or exchange transfusions, neonates and children with underlying renal disease at higher risk of hyperkalemia, patients undergoing intrauterine transfusions, or patients with hemoglobinopathies requiring chronic transfusion support.[8,9]

Conclusion

A restrictive transfusion threshold is safe in most clinical settings. Standard practice should be to initiate a transfusion with one unit of RBCs and then check the 15-minute post-transfusion hemoglobin to determine the need for additional transfusions.[10] Restrictive RBC transfusion thresholds were not associated with higher rates of adverse clinical outcomes, including 30-day mortality, myocardial infarction, cerebrovascular accident, re-bleeding, pneumonia, or thromboembolism.[3] Current blood banking practices of using standard-issue blood should be continued (but it should be noted that only a small proportion of RBC units transfused were stored for 36-42 days, the current extremes of dating).[3]

References

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