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**Objective:** To review the findings and discuss the implications of transfusion strategies in stable critically ill children.


**Findings:** In this prospective, randomized, controlled, noninferiority trial the authors compared a liberal transfusion strategy, using a transfusion threshold of 9 g/dL, to a conservative transfusion strategy, using a transfusion threshold of 7 g/dL. The primary end point was multiple organ dysfunction syndrome (MODS) or progression of MODS. The authors found that when comparing the restrictive transfusion strategy to the liberal strategy, the absolute risk reduction for developing new or progressive MODS was only 0.4% (95% confidence interval, −4.6–5.5). Using the restrictive protocol, the number needed to treat to prevent one red blood cell (RBC) transfusion was only two. The number of RBC units per patient in the restrictive group was 0.9, and in the liberal group was 1.7 (p < 0.001). When comparing the two strategies there was a relative reduction of 96% in the number of patients who had any transfusion exposure and a relative decrease of 44% in the number of transfusions administered in the restrictive strategy.

**Conclusions:** Using a restrictive transfusion protocol with a transfusion threshold of 7 g/dL in stable critically ill children is as safe as using a liberal protocol and can decrease the number of patients exposed to RBC transfusions. (Pediatr Crit Care Med 2009; 10:393–396)

**Key Words:** pediatric intensive care; red blood cell transfusion; erythrocyte

**CLINICAL SCENARIO**

A previously healthy 12-year-old boy presents to your hospital’s emergency room in status epilepticus. His seizures were refractory to the first line of therapy and you are called to the emergency room to assist in the management of this child. Upon arrival to the emergency room, you find that the patient remains in status epilepticus and is now having brief periods of apnea. At this time, you intubate the child and take him immediately to the pediatric intensive care unit (PICU). After an extensive workup, your presumed diagnosis is viral encephalitis. The patient requires continuous infusions of propofol and midazolam to control his seizures, and subsequently remains intubated. Throughout his course, the patient remains hemodynamically stable. On PICU day number four, the resident caring for the child reports that the patient’s hemoglobin has slowly drifted down from 11 g/dL to 8.5 g/dL. Understanding that critically ill patients are prone to anemia and that red blood cell (RBC) transfusions may be associated with significant risk factors, the resident asks you what the appropriate transfusion threshold is in this patient.

**FINDING THE EVIDENCE**

You explain to the resident that the justification for transfusion, based on your institution’s guidelines, is a hemoglobin of 8 g/dL in stable PICU patients, but that you are unaware of the evidence supporting these guidelines. You decide to investigate this further with the resident after rounds. You begin your search by going to the National Institute of Health PubMed site (www.pubmed.gov), and entering “transfusion thresholds for critically ill patients” in the search criteria. This search yields 21 results. You further limit your search to all children 0–18 years of age, which yields two results. One of these is a large prospective, randomized, controlled, noninferiority trial comparing a restrictive and a liberal transfusion strategy in stable critically ill children: Lacroix et al: Transfusion Strategies for Patients in Pediatric Intensive Care Units. N Engl J Med 2007; 356:1609–1619. This article seems to address your particular question and you begin to analyze the study to determine whether the data are truly applicable to your patient.

**CRITICAL APPRAISAL**

**What Is Being Studied?**

The **Study Objective.** The objective of this study was to determine whether a restrictive strategy, using a lower threshold for transfusion, was as safe as a liberal strategy for stable patients in PICU.

The **Study Design.** This was a prospective, randomized, controlled, noninferiority trial of critically ill, yet stable children in PICU.

The **Patients Included.** Patients were eligible for this study if, during their first 7 days of admission to an intensive care unit (ICU), they had a hemoglobin level ≤9.5 g/dL. A total of 5399 patients met these criteria and were evaluated for this study.

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The Patients Excluded. Patients were excluded if the expected length of stay was <24 hours, predicted survival of <24 hours, a decision to withdraw or withhold critical care, there was no physician approval, <3 days old, >14 years old, weight <3 kg, unstable hemodynamics, acute blood loss, cardiovascular problems, never discharged from the neonatal ICU, postconceptional age <40 weeks, had hemolytic anemia, severe thrombocytopenia, hypoxemia, previous enrollment into this and other studies, brain death, extracorporeal membrane oxygenation, hemofiltration, blood exchange transfusion, plasmapheresis, an inability to receive blood products, and pregnancy. A total of 4372 patients were excluded based on these criteria. Of note, hemodynamic stability was defined as mean arterial pressure not <20 mmHg below the normal mean for age, and no changes in cardiovascular treatments for at least 2 hours before enrollment.

The Interventions Compared. The study compared a liberal versus a restrictive transfusion strategy. In the restrictive strategy limb, the threshold to transfuse was hemoglobin of 7 g/dL with a target range of 8.5–9.5 g/dL. In the liberal strategy limb, the threshold to transfuse was 9.5 g/dL with a target range of 11–12 g/dL. Only prestorage leukocyte reduced RBC units were used in this study. Each protocol was applied for up to 28 days of the ICU stay, or until death.

The Outcomes Evaluated. The primary outcome of this study was powered to measure an absolute reduction of 10% in the risk of the development or progression of multiple organ dysfunction syndrome (MODS). In the “Methods” section, the authors also mentioned that mortality during the 28 days after randomization was also a primary outcome; however, because of the overall low mortality rate among children, this study was not powered to measure this outcome. In the results, mortality was reported as a secondary outcome. Other outcomes evaluated were the pediatric logistic organ dysfunction score, sepsis, transfusion reactions, nosocomial respiratory infections, catheter-related infections, adverse events, and length of ICU stay.

Are the Results of the Study Valid? Primary Questions

Was the Assignment of Patients to Treatments Randomized? Yes. Patients were randomized to each study group in blocks of two or four, which were randomly distributed and stratified according to age. The three age groups into which the patients were stratified were <28 days of age, 28–364 days of age, and greater than 365 days of age.

Were all Patients Who Entered the Trial Properly Accounted for and Attributed at its Conclusion?

Was the Follow-up Complete? Follow-up was complete in this study. Of the 626 patients in the study, only 11 (2%) were lost to follow-up. As the authors pointed out, this rate of loss was small enough to prevent any bias from sample size slippage.

Were Patients Analyzed in the Groups to Which They Were Randomized? Yes. Analysis of the primary and secondary outcomes was based on an intention-to-treat analysis. The intention-to-treat analysis is designed to measure the original intention of the treatment protocol. Recognizing that in “real-life” patients are not always in complete compliance with treatment protocols, this analysis measures the intention of the treatment protocol, but not necessarily the effects of the therapy itself. The authors of this study anticipated that some patients would be unable to fully comply with the protocol. Individual protocol suspension was left to the judgment of the attending physicians during periods of instability. In this study, adherence was defined as the proportion of days the hemoglobin concentration was kept above the threshold. Patients were considered adherent if the hemoglobin level was kept above the specific protocol’s threshold for at least 80% of the time. The intention-to-treat analysis accounted for all the patients in each protocol regardless of adherence. Because the intention-to-treat analysis could potentially account for a significant number of patients who did not meet the adherence criteria, the authors also conducted a per protocol analysis. A per-protocol analysis is designed to measure the true efficacy of the therapy, and only takes into account patients who meet the adherence criteria.

Secondary Questions

Were Patients, Health Workers, and Study Personnel “Blind” to Treatment? No. Because of the nature of this study model, the healthcare workers involved in the treatment of the patients could not be blinded.

WHAT WERE THE RESULTS?

How Large was the Treatment Effect?

The treatment effect, based on the results of the intention-to-treat analysis, was not statistically or clinically significant. The absolute risk reduction for developing new or progressive MODS was only 0.4% (95% confidence interval [CI], 0.04–5.5) in favor of the restrictive strategy. When new or progressive MODS were stratified according to age, country, and severity of illness, there was still no significant reduction in the risk for development or progression of MODS. The results of the per-protocol analysis were quite similar to the results of the intention-to-treat analysis. The absolute risk reduction in the per-protocol analysis was 0.8% (95% CI, 0.3–5.9).

The authors also conducted a time-to-event analysis using Kaplan-Meier curves and the log-rank test. Time-to-event data are used in survival analysis and when the outcome of interest is the time to a certain event, in this case the onset or progression of MODS (1). A hazard ratio was generated from the time-to-event analysis. The hazard ratio, which is essentially an estimate of the relative risk, demonstrated a ratio of 0.95 for the restrictive transfusion strategy. A hazard ratio of 0.95 suggests that there was no increase
in risk for the onset or progression of MODS when using the restrictive strategy, compared with the liberal strategy. The greatest absolute difference in risk of new or progressive MODS occurred when the two strategies were compared in the patients for whom the protocol was suspended. The authors suggested that the protocol was suspended for more patients in the restrictive strategy group, because of the uneasiness of attending physicians in keeping the hemoglobin so low in critically ill children. Among patients for whom the protocol was suspended, the restrictive strategy group had an absolute risk reduction in the development/progression of MODS of 18.9% (95% CI, –7.3–45); however, this was not statistically significant.

How Precise Was the Estimate of the Treatment Effect?

One of the strongest points of this study was the number of patients enrolled and the subsequent precision of the CI. The authors hypothesized that a restrictive strategy would not be inferior to a liberal strategy if the limits of the 95% CIs did not exceed 10%. As stated above, the absolute risk reduction for the primary outcome using the restrictive strategy was only 0.4%, and using the 95% CI the range was –4.6% to 5.5%. When new or progressive MODS was stratified according to age, country, and severity of illness, only the patients with pediatric risk of mortality scores in the highest quartile had and upper limit of the 95% CI that exceeded 10% (–11.1% to 15.9%) in favor of the restrictive strategy group. This particular group exceeded the threshold of 10% set by the authors. These data suggest that the absolute risk reduction of new or progressive MODS in the most severely ill patients could be as much as 11.1% or an absolute risk increase of 15.9% with 95% confidence. There were no other CIs whose upper limits exceeded 10%.

Using the restrictive protocol, the number needed to treat to prevent one RBC transfusion was only two. The number of RBC units per patient in the restrictive group was 0.9, and in the liberal group was 1.7 (p < 0.001). Comparing the two strategies there was a 96% relative reduction in the number of patients who had any transfusion exposure and a 44% relative decrease in the number of transfusions administered in the restrictive strategy.

Will the Results Help Me in Caring for My Patients?

Can the Results Be Applied to My Patient Care? Yes, the patients evaluated in this study are similar to those in most busy multidisciplinary PICUs. Evidence suggests that critically ill patients may be prone to anemia for several reasons. In addition to hemodilution and phlebotomy there appears to be a significant suppression of hematopoiesis regulated by inflammatory cytokines, a blunted response to endogenous erythropoietin, and nutritional deficiencies (2–4). Adult studies have shown that up to 95% of ICU patients have a hemoglobin level below normal by ICU day 3 (5).

There also seems to be a mounting body of evidence suggesting that RBC transfusions are associated with significant risk factors such as immunosuppression and nosocomial bloodstream infections (6–10). Interestingly, the immunosuppressive effects of RBC transfusions have been considered since the 1970s when it was noted that kidney transplant patients receiving RBC transfusions had improved allograft survival (10). A relatively recent prospective cohort study performed over 2000 adult ICU patients showed that RBC transfusions were a significant risk factor for nosocomial bloodstream infections even when corrected for survival probability. Using leukoreduced RBCs decreased the risk of infection slightly, but not significantly (8). Another prospective cohort study, performed on over 2000 pediatric ICU patients, showed that a higher number of RBC transfusions was associated with an increased risk of bloodstream infections (9).

A large retrospective study of over 8000 adults after cardiac surgery showed that RBC transfusions were not only associated with infections but also postoperative ischemia including myocardial infarction, stroke, and renal failure (11). This observation is quite significant because it suggests that even in anemic adult patients, RBC transfusions may actually decrease oxygen delivery to vital tissues, a result that is converse to the primary intention of RBC transfusions. An explanation for this phenomenon may be found in the progressive changes that occur in stored RBCs, known as the storage lesion (12).

It has been accepted for some time that the storage of RBCs causes physiologic changes within the erythrocyte including alterations in the morphology and deformability of the corpuscle, and depletion of important compounds such as 2,3-diphosphoglycerate (12). These changes may effectively decrease oxygen delivery either by limiting the ability of the RBC to enter the microcirculation or by increasing the hemoglobin-oxygen affinity. Recently a study from Duke demonstrated several additional adverse changes in stored RBCs including the rapid decline in S-nitrosohemoglobin (SNO-Hb), a compound essential to the RBCs ability to affect hypoxic vasodilation and thus improve tissue oxygenation (13). SNO-Hb functions as an oxygen sensor in the RBC by donating nitric oxide in regions of hypoxia, causing local vasodilation and a subsequent increase in oxygen delivery. This study showed that after only 3 hours of storage, SNO-Hb levels had fallen significantly and remained low throughout a 42-day storage period. Another study, also from Duke, went on to demonstrate that in both in vitro and in vivo experiments, stored RBCs that are deplete of SNO-Hb have a diminished ability to affect hypoxic vasodilation (14).

Based on the results of these studies it appears that the depletion of SNO-Hb may be yet another mechanism by which stored RBCs could negatively affect oxygen delivery.

In the Lacroix study, decreasing the transfusion threshold from 9 g/dL to 7 g/dL significantly decreased the number of transfusions. Furthermore, the number needed to treat to reduce one transfusion was only two patients. By using a lower transfusion threshold, we can significantly decrease the number of blood transfusions and, therefore, limit any potential adverse outcomes.

Based on the results of the Lacroix study, it appears to be safe to use a conservative or liberal transfusion threshold for stable children in the PICU, with respect to the designated outcomes. Considering that the CI did range from –11.1% to 15.9% in patients with pediatric risk of mortality scores ≥8, we may need to be cautious in using a liberal transfusion protocol in this subset of critically ill patients. An increase in the absolute risk of nearly 16% could be clinically meaningful in patients with the highest quartile pediatric risk of mortality scores.

It was not the purpose of this study to look at safe transfusion thresholds in unstable, critically ill children. Understandably, it would be nearly impossible to
determine what the safe transfusion threshold is for unstable PICU patients. The pathophysiologic causes of instability in our patients are too numerous. However, by only looking at stable children, a great number of our patients are excluded by this study. Of the 5399 patients eligible for the study, 81% were excluded before the screening process because of the multiple exclusion criteria. Similarly, when these exclusion criteria are applied to our average patient population, many would not qualify. We are then left with other guidelines, such as early goal-directed therapy (15), and the clinical practice parameters for the support of pediatric patients in septic shock (16), which have significantly higher transfusion thresholds. In light of the current evidence suggesting the potential adverse effects of RBC transfusions, studies are underway to critically evaluate these guidelines. In any case, as our unstable patients progress to a more stable condition, we can then transition them to a restrictive transfusion strategy.

Were all Clinically Important Outcomes Considered? The authors were careful to consider all of the potential short-term outcomes, but it did not look at any of the potential long-term outcomes. The study by Jonas et al (17), which connected a lower hematocrit during cardiopulmonary bypass to poorer neurodevelopmental outcomes, should at least cause us to question how a lower hematocrit in a stressed critically ill child affects long-term neurodevelopment.

Are the Likely Treatment Benefits Worth the Potential Harms and Costs? This study succeeded in determining that a restrictive transfusion strategy is as safe as a liberal transfusion strategy. To then recommend that we adopt a universal restrictive strategy in stable critically ill children, who may be prone to significant anemia, presupposes that there is a benefit to using fewer blood transfusions. Classic teaching has always stressed that we should not transfuse patients unnecessarily because of the risk of transfusion related infections, transfusion reactions, and the unnecessary use of a limited blood supply. With the institution of leukocyte-reduced RBCs, complications with RBC transfusions may have been reduced—however, they still exist (18). Even though this study could not show a significant difference in the number of transfusion reactions, there were certainly more in the liberal strategy group than in the restrictive strategy group (2% vs. 1%). If this study could have been powered to look at such an end point, it is likely that there would have been a significant difference, given the substantial reduction in the total number of transfusions. Considering emerging data within the literature, it appears that RBC transfusions may play a role in immunosuppression, can be an independent risk factor for nosocomial bloodstream infections, and may paradoxically decrease oxygen delivery secondary to adverse changes during storage. In view of the current evidence, it appears that the institution of a restrictive transfusion strategy in stable critically ill children is worth the potential harms and costs.

CASE CONCLUSION

Based on the results of this study this patient was not given a RBC transfusion for a hemoglobin of 8.5 g/dL. After five more days the patient’s status epilepticus finally relented and we were able to lift the sedative infusions. Two days later the patient’s mental status had significantly improved and he was extubated. The hemoglobin nadir during his PICU stay was 7.5 g/dL and he was not given any RBC transfusions. He was transferred to the floor on hospital day 12 on an oral anti-epileptic regimen.

REFERENCES