Published in final edited form as:

Pediatr Crit Care Med. 2018 September ; 19(9) : S121–S126. doi:10.1097/PCC.0000000000001620.

Recommendations on Red Blood Cell Transfusions for Critically Ill Children with Non-Hemorrhagic Shock from the Pediatric Critical Care Transfusion and Anemia Expertise Initiative

Jennifer A. Muszynski, MD, MPH^{1,2}, Nina A. Guzzetta, MD³, Mark W. Hall, MD^{1,2}, Duncan Macrae, MB, ChB⁴, Stacey L. Valentine, MD⁵, Scot T. Bateman, MD⁵, Philip C. Spinella, MD⁶, and for the Pediatric Critical Care Transfusion and Anemia Expertise Initiative (TAXI), in collaboration with the Pediatric Critical Care Blood Research Network (Blood Net) and the Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network*

¹Division of Critical Care Medicine, Nationwide Children's Hospital, Columbus, OH

²The Research Institute at Nationwide Children's Hospital, Columbus, OH

³Department of Anesthesiology, Emory University School of Medicine, Children's Healthcare of Atlanta, Atlanta, GA

⁴Pediatric Critical Care, Royal Brompton Hospital, London, UK

⁵Department of Pediatrics, University of Massachusetts Medical School, Worcester, MA

⁶Washington University School of Medicine, Department of Pediatrics, St. Louis, MO

Abstract

Objective—To present the recommendations and supporting literature for red blood cell (RBC) transfusions in critically ill children with non-hemorrhagic shock developed by the Pediatric Critical Care Transfusion and Anemia Expertise Initiative (TAXI).

Design—Consensus conference series of international, multidisciplinary experts in RBC transfusion management of critically ill children

Methods—The panel of 38 experts developed evidence-based and when evidence was lacking, expert-based clinical recommendations as well as research priorities for RBC transfusions in critically ill children. The non-hemorrhagic shock subgroup included five experts. Electronic searches were conducted using PubMed, EMBASE, and Cochrane Library (CENTRAL) databases from 1980 to May 2017. Agreement was obtained using the Research And Development/University of California, Los Angeles (RAND UCLA) appropriateness method. Results were summarized using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) method.

Corresponding Author (reprints will not be available): Jennifer A Muszynski MD, MPH, Critical Care Medicine, Nationwide Children's Hospital, 700 Children's Drive, Columbus, OH 43205, Phone: (614) 722 – 3438, Fax: (614) 722 – 3443, Jennifer.muszynski@nationwidechildrens.org.

*TAXI Members listed in Appendix 1.

Conflicts of Interest: The remaining authors have disclosed that they do not have any potential conflicts of interest.

Results—TAXI Consensus Conference experts developed and voted on a total of 4 clinical and 4 research recommendations focused on RBC transfusion in the critically ill child with non-hemorrhagic shock. All recommendations reached agreement (>80%). Of the 4 clinical recommendations, 3 were based on consensus panel expertise, while one was based on weak pediatric evidence. In hemodynamically stabilized critically ill children with a diagnosis of severe sepsis or septic shock, we recommend not administering a RBC transfusion if the Hb concentration is ≥ 7 g/dL. Future studies are needed to determine optimum transfusion thresholds for critically ill children with non-hemorrhagic shock undergoing acute resuscitation.

Conclusions—The TAXI Consensus Conference developed pediatric-specific clinical and research recommendations regarding RBC transfusion in the critically ill child with non-hemorrhagic shock. While agreement among experts was strong, available pediatric evidence was scant - revealing significant gaps in the existing literature.

Keywords

transfusion; red blood cell; consensus conference; critically ill child; shock

Introduction

Shock is defined as inadequate oxygen delivery to meet metabolic demands and is often also referred to as “oxygen debt”. Non-hemorrhagic shock, secondary to conditions such as sepsis, is a common indication for red blood cell (RBC) transfusion with the intent to increase oxygen delivery in critically ill children (1, 2). However, little data exists to guide RBC transfusion practice in this population, underscoring the need for ongoing prospective study in this area. The following article reviews the current literature and details clinical and research recommendations for RBC transfusion in critically ill children with non-hemorrhagic shock.

Methods

The details of the methodology are described elsewhere in this supplement of *Pediatric Critical Care Medicine*. Briefly, we searched PubMed, EMBASE, and Cochrane Library from 1980 to December 2015, with an update in May 2017, using a combination of medical subject heading terms and text words to define concepts of RBC transfusion and non-hemorrhagic shock in children. We searched references from identified articles for additional publications. Two authors reviewed all citations independently. We used a standardized data extraction form to construct evidence tables and graded the evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. A panel of 38 experts from 29 academic institutions in 8 countries met over the course of two years to develop evidence-based and, when evidence was lacking, expert-based recommendations for RBC transfusion in critically ill children. Five experts coordinated the non-hemorrhagic shock subgroup. Recommendations developed and supporting literature were reviewed and scored by all panel members, using the Research And Development/University of California Appropriateness Method. All recommendations reached agreement (>80%). Final recommendations for RBC transfusion in critically ill children with non-hemorrhagic shock were divided into two categories: clinical recommendations, and research recommendations.

Results

Structured literature search identified 1,827 abstracts. Of these, 1,785 references were excluded based on the abstract. An additional 39 references were excluded based on full manuscript review, leaving 3 references that were used for guideline creation. The references included are detailed in Supplemental Digital Data, Supplement Table 1. Four clinical recommendations and 4 research recommendations were developed and voted on. All recommendations reached agreement (>80%).

CLINICAL RECOMMENDATIONS

Children with non-hemorrhagic shock

Recommendations

3.1: In critically ill children with non-hemorrhagic shock, we recommend considering all possible strategies to augment oxygen delivery and decrease oxygen demand, instead of only considering RBC transfusion. *Consensus panel expertise, 97% Agreement, Median 9 IQR 8-9*

3.2: We cannot recommend a specific RBC transfusion decision making strategy using physiologic based metrics and biomarkers in critically ill children with non-hemorrhagic shock. *Consensus panel expertise, 97% Agreement, Median 8, IQR 8-9*

Rationale—Prompt recognition and reversal of shock or oxygen debt remain mainstays of adult and pediatric critical care. Since Rivers et al. in 2001, RBC transfusion, as a means to potentially increase oxygen delivery, has been an integral part of early goal directed therapy (EGDT) aimed at early shock reversal. In children, a single randomized controlled trial of 102 pediatric patients with septic shock evaluated central venous oxygen saturation (ScvO₂)-guided goal-directed therapy (3). The intervention group included continuous ScvO₂ measurement and adjusted therapies to achieve and maintain a ScvO₂ of > 70%. Per the guideline-based protocol, subjects in the intervention group with normal blood pressure and ScvO₂ < 70% were administered either crystalloid infusion, inotropic support, or RBC transfusion (if the hemoglobin level was < 10 g/dL). Accordingly, the therapeutic interventions which significantly differed between the intervention and control groups within the first 6 hours of resuscitation included crystalloid infusion (28 (20-40) ml/kg vs 5 (0-20) ml/kg); addition of inotrope (29.4% vs 7.8%); and RBC transfusion (45.1% vs. 15.7%). The study demonstrated reduced 28-day mortality (11.8% vs. 39.2%, adjusted OR 0.18, 95% CI: 0.05-0.69) in the intervention group, suggesting benefit to ScvO₂-guided, goal-directed therapy. However, because the evaluated interventions were applied within a bundle, the relative effects of RBC transfusion compared to crystalloid infusion or inotropic support cannot be determined. To date, no studies have been performed to evaluate the efficacy of RBC transfusion compared to alternate methods to reverse shock or to augment oxygen delivery in this population.

RBC transfusion carries risk. While the incidences of blood-borne infection, hemolytic transfusion reaction, and non-hemolytic transfusion reactions are low, RBC transfusion likely also confers risk of morbidity and mortality due to transfusion-related immune

modulation, dysregulated hemostasis, and transfusion-associated lung injury (4). Critically ill patients with septic shock may be at particularly high risk of transfusion-associated complications because of their underlying states of dysregulated hemostatic and immunologic responses at the time of transfusion (5-9). In a recent meta-analysis of cohort studies in critically ill septic adults, RBC transfusion was associated with increased risks of nosocomial infection, acute lung injury, and renal injury (10). In critically ill children, RBC transfusion is associated with prolonged mechanical ventilation, intensive care unit (ICU) stay, and new or progressive organ dysfunction (11). While prospective studies to determine relative risks and benefits of RBC transfusion compared to therapeutic alternatives to augment oxygen content or delivery are lacking, it is possible that for some children with non-hemorrhagic shock, transfusion risks may outweigh benefits.

At this time given the known risks of transfusion, it seems prudent to consider RBC transfusion as part of a more comprehensive approach to augment the ratio of oxygen delivery to oxygen demand. Future studies evaluating RBC transfusion as part of a tiered approach to shock management are needed.

The primary goal for RBC transfusion in patients with non-hemorrhagic shock and anemia is to augment arterial oxygen content in order to enhance oxygen delivery to tissues. It is therefore likely that using markers of oxygen debt and delivery to guide RBC transfusion decision-making would be superior to using hemoglobin measurements alone. Such markers would be expected to have the added advantage of assessing RBC transfusion efficacy. While several candidate markers exist (including central venous oxygen saturation, lactate measurements, near-infrared spectroscopy, invasive measures of oxygen consumption and delivery, etc.), clear superiority of one measure over another has yet to be determined. Accordingly, clinical trials evaluating outcomes related to the use of physiologic-based transfusion triggers in children with non-hemorrhagic have yet to be performed. Therefore, while physiologic-based triggers for RBC transfusion in the setting of shock hold promise for the future, at this time we cannot recommend one strategy over another.

Hemodynamically unstable children with non-hemorrhagic shock

Recommendation

3.3: We cannot make a recommendation regarding transfusion thresholds for critically ill children with unstable non-hemorrhagic shock. *Consensus panel expertise, 100% Agreement, Median 9, IQR 8-9*

Rationale—RBC transfusion strategy has not been evaluated in prospective studies of critically ill children with unstable shock. Current American College of Critical Care Medicine (ACCM) guidelines for hemodynamic support of pediatric and neonatal shock recommend RBC transfusion to a goal hemoglobin of > 10g/dL to achieve a central venous oxygen saturation > 70% (12). The recommendation is based on the de Oliveira study, in which an ScvO₂-guided resuscitation (which included RBC transfusion for ScvO₂ < 70% and hgb < 10g/dL) demonstrated a significant mortality benefit compared to non-ScvO₂-guided resuscitation - suggesting that, at least as part of a bundled goal-directed resuscitation strategy, there may be benefit to this transfusion threshold (3). However, as discussed above,

the ScvO₂-targeted group also received significantly greater fluid resuscitation in the first 6 hours and were more likely to have early initiation of inotropic support – both of which were likely beneficial. Thus, it is unclear whether the mortality benefit seen was related to the RBC transfusion strategy.

To date, randomized trials of liberal versus restrictive RBC transfusion practice in the acute shock setting are lacking. The only RCT in critically ill children, the TRIPICU study, excluded hemodynamically unstable children (13). In adults, the TRISS trial included subjects with shock; however, the median time from ICU admission to enrollment was approximately 24 hours, and 12% of otherwise eligible subjects were excluded due to prior transfusion (14). Thus, the effects of a restrictive transfusion strategy in the early hours of acute resuscitation remain unclear. Indeed, in a propensity-score matched retrospective analysis of an adult multicenter early goal-directed therapy registry, RBC transfusion was independently associated with improved mortality for those patients with central venous oxygen saturation < 70% and hemoglobin < 10 gm/dl while inotrope infusion was not. These data suggest that RBC transfusion may be beneficial in this setting, though definite conclusions cannot be drawn due to the limitations of the retrospective study design (15).

The rationale for RBC transfusion in the setting of unstable shock is to improve oxygen consumption by augmenting hemoglobin concentration and thereby increasing oxygen delivery. Two small studies have evaluated the effects of RBC transfusion on oxygen delivery and consumption in pediatric patients with septic shock – with conflicting results (16, 17). In both studies, RBC transfusion was associated with increased oxygen delivery. In the Mink et al study (n = 8), RBC transfusion was not associated with increase in oxygen consumption (17). By contrast, the Lucking et al study (n = 7), which included only children with hyperdynamic shock and a low baseline oxygen consumption, demonstrated statistically significant improvement in oxygen consumption post RBC transfusion (VO_2 112 ± 36 vs. 157 ± 60 ml/min*m²; $p < 0.01$) (16). The pre-transfusion hemoglobin in the Lucking et al study was 9.3 ± 1.4 g/dL. These studies suggest that for select children with septic shock, even in the absence of severe anemia, RBC transfusion may improve oxygen consumption – though effects on clinical outcomes are unclear.

While a specific recommendation cannot be made, until further studies are conducted, it is reasonable to consider a hemoglobin threshold that ranges between <7 and <10 g/dL as part of a comprehensive approach to improve oxygen delivery for children with unstable non-hemorrhagic shock and evidence of oxygen debt.

Hemodynamically stabilized children with non-hemorrhagic shock

Recommendation

3.4: In hemodynamically stabilized* critically ill children with a diagnosis of severe sepsis or septic shock, we recommend not administering a RBC transfusion if the Hb concentration is ≤ 7 g/dL. *Weak recommendation, Low quality pediatric evidence (2C), 96% Agreement, Median 8, IQR 8-9*

*Hemodynamically stabilized is defined according to inclusion criteria for the Transfusion strategies for patients in Pediatric Intensive Care Units (TRIPICU) study: mean systolic

blood pressure not less than 2 standard deviations below the mean normal for age and cardiovascular treatments not increased within the past 2 hours (13).

Rationale—A single randomized controlled trial (RCT) of restrictive versus liberal transfusion strategies in critically ill children exists. The TRIPICU study was a randomized, controlled non-inferiority study evaluating a liberal (transfusion threshold hemoglobin of 9.5g/dl) versus restrictive (transfusion threshold of 7 g/dl) transfusion strategy in 637 critically ill children (13). All patients included in the TRIPICU study were hemodynamically stabilized as defined by mean systolic blood pressure not less than 2 standard deviations below the mean normal for age and cardiovascular treatments not increased within the past 2 hours. One-hundred-and-thirty-seven patients with sepsis were included in TRIPICU and were analyzed as a planned subgroup analysis (18). Of these, 40 subjects had severe sepsis (19 restrictive; 12 liberal) and 34 subjects had septic shock (13 restrictive; 21 liberal). Across the entire 137 subject cohort (69 restrictive; 68 liberal), the proportion of patients who developed new or progressive multiple organ dysfunction (NP-MODS) was the same between groups (ARR: 0.3%; 95%CI: -12%, +14%). PICU mortality and 28-day mortality were higher in the restrictive group (5 vs 2 deaths, $p = 0.44$; and 7 vs 2, $p = 0.08$, respectively), though the number of deaths was small and differences were not statistically significant. This does however raise the possibility of harm in the restrictive group, which should be evaluated in additional study. It is also important to consider that only a portion of the analyzed subgroup had septic shock and were on vasoactive support. The results of Karam et al. have yet to be verified in larger study of critically ill children with severe sepsis or septic shock, which represents an important research need.

Extrapolating from adult literature, The Transfusion Requirements in Septic Shock (TRISS) trial randomized 998 adults with septic shock to a transfusion threshold hemoglobin of 7 g/dL versus 9 g/dL (14). In contrast to the TRIPICU trial, hemodynamically unstable patients were included the TRISS trial. There were no differences in the primary outcome of 90 day mortality between groups (relative risk, 0.94; 95% CI 0.78-1.09), suggesting that a restrictive transfusion strategy was safe within their study population. In a follow up study, there were also no significant differences between groups in 1 year mortality or in health-related quality of life at 1 year (19). Overall, these studies suggest that a hemoglobin threshold of 7 g/dL is safe in critically ill patients with shock, particularly once they are stabilized, though larger studies in children with shock are needed. *GRADE 2C based on downgrading for risk of bias, imprecision and residual confounding.*

RECOMMENDATIONS FOR RESEARCH

Recommendations

R3.1—We recommend future studies to evaluate the utility of physiologic markers of oxygen debt and oxygen delivery in conjunction with hemoglobin-based targets to guide RBC transfusion decisions for critically ill children with non-hemorrhagic shock. *Consensus panel expertise, 97% Agreement, Median 9, IQR 8-9*

R3.2—We recommend future studies to determine optimum transfusion thresholds for critically ill children with non-hemorrhagic shock undergoing acute resuscitation. *Consensus panel expertise, 97% Agreement, Median 9, IQR 8-9*

R3.3—The relative risks, benefits and alternatives of RBC transfusion to augment oxygen delivery remain unclear and should be the subject of future studies in critically ill children with non-hemorrhagic shock. *Consensus panel expertise, 97% Agreement, Median 9, IQR 8-9*

R3.4—We recommend future studies to determine long-term effects of anemia in children with non-hemorrhagic shock. *Consensus panel expertise, 100% Agreement, Median 9, IQR 8-9*

Rationale

As discussed above, the evidence guiding RBC transfusion practice in children with non-hemorrhagic shock is limited; and many questions remain. Chief among them is whether hemoglobin levels are the most appropriate triggers for RBC transfusion, particularly for children undergoing resuscitation for acute shock. Given that the purpose for RBC transfusion in this setting is to augment oxygen delivery to match oxygen demand, it seems reasonable that measures of inadequate oxygen delivery may provide more clinically relevant transfusion triggers. Several candidate markers exist. However, it is unclear which of these markers will best predict need for transfusion, and prospective studies evaluating physiology-based markers to guide RBC transfusion decision-making have not been performed. Similarly, studies evaluating RBC transfusion compared to other interventions to augment oxygen delivery for those patients with demonstrated oxygen debt are needed. It is possible that the risk/benefit ratio of alternative approaches to augment oxygen delivery (*e.g.* augmenting inotropic support) is more favorable compared to that of RBC transfusion, though this remains an unanswered question.

Studies to date evaluating RBC transfusion practice in critically ill children have focused on short-term outcomes (13, 20, 21). As such, relationships between RBC transfusion and long-term outcomes, including neurodevelopmental outcomes, are unknown. Because the majority of critically ill children survive their acute illness, it is increasingly important to understand effects of ICU-based interventions on long term outcomes. Additionally, infants and children are exposed to critical illness at a time of maximal brain growth and development, underscoring the need to understand effects of RBC transfusion and other therapies on neurodevelopmental outcomes. Relevant to RBC transfusion, randomized trials of liberal versus restrictive transfusion thresholds in premature infants reveal mixed results regarding neurodevelopmental outcomes and it is unclear which strategy may be preferred (22-25). While the ongoing Transfusion of Prematures (TOP) trial [NCT01702805] promises to shed light on this important question, it is unclear whether these findings will be generalizable to full term infants and children in the pediatric ICU.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank all members of the TAXI initiative for their support and their comments. The study was supported by grants from the University of Massachusetts, CHU Sainte-Justine Foundation, National Institute of Child Health Development (1 R13 HD088086-01), National Heart, Lung and Blood Institute, Washington University Children's Discovery Institute (DCI-E1-2015-499) and the Society for the Advancement of Blood Management. We also thank the World Federation of Pediatric Intensive and Critical Care Societies, Society for Critical Care Medicine and the AABB for their support of TAXI.

Sources of Funding:

The Transfusion and Anemia Expertise Initiative was supported by the Eunice Kennedy Shriver National Institute of Child Health and Human Development and National Heart, Lung, and Blood Institute under award number 1 R13 HD088086-01, Society for the Advancement of Blood Management SABM-Haemonetics Research Starter Grant, CHU-Sainte-Justine Foundation, Washington University Children's Discovery Institute (DCI-E1-2015-499) and the University of Massachusetts Medical School.

Copyright form disclosure: Dr. Muszynski is supported by K08HL 123925. Dr. Bateman's institution received funding from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) and National Heart, Lung, and Blood Institute (NHLBI) R13 grant and the Society for the Advancement of Blood Management (SABM), and he received funding from the National Institutes of Health (NIH). Dr. Valentine's institution received funding from NICHD and NHLBI under award number 1 R13 HD088086-01; the SABM SABM-Haemonetics Research Starter Grant; and Washington University Children's Discovery Institute (DCI-E1-2015-499). She received other support from CHU-Sainte-Justine Foundation and the University of Massachusetts Medical School, and she received support for article research from the NIH, SABM SABM-Haemonetics Research Starter Grant, CHU-Sainte-Justine Foundation, Washington University Children's Discovery Institute, and the University of Massachusetts Medical School. Dr. Spinella received funding from New Health Sciences.

Appendix 1: Pediatric Critical Care Transfusion and Anemia eXpertise Initiative (TAXI) Members

(* for Executive Committee) Co-chairs: Stacey L. Valentine MD MPH* and Scot T. Bateman MD*, *University of Massachusetts, USA*, Content Experts: Section 1. General pediatric critical care patient based on physiologic and hemoglobin thresholds: Andrew Argent MD MBBCh, *University of Cape Town, South Africa*, Jeffrey L. Carson MD, *Rutgers Robert Wood Johnson Medical School, USA*, Jill M. Cholette MD*, *University of Rochester, USA*, Allan Doctor MD*, *Washington University of St. Louis, USA*, Jacques Lacroix MD*, *Université de Montréal, Canada*, Kenneth Remy MD, *Washington University of St. Louis, USA*, Section 2. Respiratory failure: Pierre Demaret MD MSc, *CHC Liege, Belgium*, Guillaume Emeriaud MD PhD, *Université de Montréal, Canada*, Nabil E. Hassan MD, *University of Illinois, USA*, Martin C.J. Kneyber MD PhD, *University of Groningen, Netherlands*, Marisa Tucci MD*, *Université de Montréal, Canada*, Section 3. Shock, excluding hemorrhagic shock: Nina Guzzetta MD, *Emory University, USA*, Mark W. Hall MD, *Ohio State University, USA*, Jennifer A. Muszynski MD MPH, *Ohio State University, USA*, Philip C. Spinella MD, *Washington University of St. Louis, USA*, Duncan Macrae MB ChB, *Imperial College London, UK*, Section 4. Hemorrhagic shock and non-life-threatening bleeding, Oliver Karam MD PhD, *Virginia Commonwealth University*, Robert T. Russell MD MPH, *University of Alabama, USA*, Philip C. Spinella MD*, *Washington University of St. Louis, USA*, Paul Stricker MD, *University of Pennsylvania, USA*, Adam M. Vogel MD, *Texas Children's Hospital, USA*, Section 5. Acute brain injury: Philip C. Spinella MD*, *Washington University of St. Louis, USA*, Robert C. Tasker MA MD MBBS, *Harvard University, USA*, Alexis F. Turgeon MD MSc, *Université Laval, Canada*, Section 6.

Acquired or congenital heart disease, Jill M. Cholette MD*, *University of Rochester, USA*, Steven M. Schwartz MD, *University of Toronto, Canada*, Ariane Willems MD, *University of Brussels, Belgium*, [Section 7](#). Sickle cell/oncologic disease, Cassandra D. Josephson MD, *Emory University, USA*, Naomi LC Luban MD, *George Washington University, USA*, Leslie E. Lehmann MD, *Harvard University, USA*, Robert I. Parker MD*, *Stony Brook University, USA*, Simon J. Stanworth MD, *NHS Blood and Transplant, Oxford, UK*, Marie E. Steiner MD MS*, *University of Minnesota, USA*, Nicole D. Zantek MD PhD, *University of Minnesota, USA*, [Section 8](#). Receiving support from extracorporeal, ventricular assist and renal replacement therapy devices: Melania M. Bembea MD PhD*, *Johns Hopkins University, USA*, Timothy Bunchman MD, *Virginia Commonwealth University, USA*, Ira M. Cheifetz MD, *Duke University, USA*, James Fortenberry MD, *Emory University, USA*, Marie E. Steiner MD MS*, *University of Minnesota, USA*, [Section 9](#). Selection and processing of red blood cell components: Meghan Delaney DO, MPH, *Children's National Health System USA*, Cassandra D. Josephson MD, *Emory University, USA*, Robert I. Parker MD*, *Stony Brook University, USA*, Leo van de Watering MD, *Leiden University, Netherlands*, Nicole D. Zantek MD PhD, *University of Minnesota, USA*, [Evidence-Based Medicine](#): Karen A. Robinson PhD, *Johns Hopkins University, USA*, Melania M Bembea MD PhD*, *Johns Hopkins University, USA*, [Implementation Science](#): Sara Small MS, *Washington University of St. Louis, USA*, Katherine Steffen MD, *Stanford University, USA*

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SUMMARY

Clinical evidence to guide RBC transfusion decision-making for children with non-hemorrhagic shock remains sparse, resulting in recommendations based on only weak evidence or consensus expert opinion. While consensus was reached with strong agreement, much work remains to answer important questions about the safety and efficacy of RBC transfusion in this patient population.