Consensus Recommendations for RBC Transfusion Practice in Critically Ill Children From the Pediatric Critical Care Transfusion and Anemia Expertise Initiative

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Objectives: To date, there are no published guidelines to direct RBC transfusion decision-making specifically for critically ill children. We present the recommendations from the Pediatric Critical Care Transfusion and Anemia Expertise Initiative.

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

Setting: Not applicable.

Intervention: None.

Subjects: Children with, or children at risk for, critical illness who receive or are at risk for receiving a RBC transfusion.

Methods: A panel of 38 content and four methodology experts met over the course of 2 years to develop evidence-based, and when evidence lacking, expert consensus-based recommendations regarding decision-making for RBC transfusion management and research priorities for transfusion in critically ill children. The experts focused on nine specific populations of critically ill children: general, respiratory failure, nonhemorrhagic shock, nonlife-threatening bleeding or hemorrhagic shock, acute brain injury, acquired/congenital heart disease, sickle cell/oncology/transplant, extracorporeal membrane oxygenation/ventricular assist/ renal replacement support, and alternative processing. Data to formulate evidence-based and expert consensus recommendations were selected based on searches of PubMed, EMBASE, and Cochrane Library from 1980 to May 2017. Agreement was obtained using the Research and Development/UCLA Appropriateness Method. Results were summarized using the Grading of Recommendations Assessment, Development, and Evaluation method.

Measurements and Results: The Transfusion and Anemia Expertise Initiative consensus conference developed and reached consensus on a total of 102 recommendations (57 clinical [20 evidence based, 37 expert consensus], 45 research recommendations). All final recommendations met agreement, defined a priori as greater than 80%. A decision tree to aid clinicians was created based on the clinical recommendations.

Conclusions: The Transfusion and Anemia Expertise Initiative recommendations provide important clinical guidance and applicable tools to avoid unnecessary RBC transfusions. Research recommendations identify areas of focus for future investigation to improve outcomes and safety for RBC transfusion. (*Pediatr Crit Care Med* 2018; 19:884–898)

Key Words: blood; child; consensus development conference; pediatric critical care; red blood cell; transfusion

Anemia is common in critically ill children and is observed in 74% of patients with a length of stay in a PICU over 2 days (1). Anemia tolerance in this population has not been well studied. The transfusion of RBCs in the form of RBC units or whole blood units can be lifesaving in hemorrhagic shock as well as in critically ill children with severe anemia (hemoglobin levels < 5.0 g/dL) (2–6). The immediate goal of RBC transfusion is to increase the hemoglobin concentration of recipients, with the intent to improve oxygen delivery and oxygen consumption (7, 8). However, over time, RBC storage may reduce oxygen delivery capacity to deliver oxygen, and RBC transfusion has been associated with morbidities and mortality, especially in the critically ill, raising important safety concerns (9). Although infectious risks are low, noninfectious serious hazards of transfusion (NISHOT), such as transfusion-associated lung injury and transfusion-associated circulatory overload, are much more prevalent in critically ill children (10–14). Therefore, due to the risks of complications and the increased morbidity associated with transfusions, efforts are needed to ensure appropriate RBC transfusions decision-making.

Using a more restrictive or lower hemoglobin threshold for RBC transfusion decision-making has been studied in critically ill children. In 2007, Lacroix et al (15) published the pivotal Transfusion strategies for Patients in PICUs (TRIPICU) study, which compared a restrictive (hemoglobin ≤ 7.0 g/dL) to a liberal transfusion (hemoglobin ≤ 9.5 g/dL) threshold in hemodynamically stable critically ill children. This multicenter international randomized controlled trial (RCT) enrolled 637 PICU patients and demonstrated that the restrictive transfusion strategy was as efficacious as liberal transfusion strategy based on similar new or progressive multiple organ dysfunction rates between study groups. Furthermore, limiting RBC transfusion to children with hemoglobin level less than or equal to 7.0 g/L reduced RBC transfusion frequency by half. An RCT published by Cholette et al (16) that compared a restrictive versus liberal RBC transfusion strategy (< 9.0 vs < 13.0 g/dL) in 60 children with cyanotic univentricular physiology also showed that a restrictive strategy was noninferior and reduced exposure to RBC transfusions. These seminal studies provide evidence that certain populations of critically ill children benefit from a restrictive approach toward RBC decision-making.

Despite evidence that a restrictive transfusion strategy in hemodynamically stable children is noninferior to a liberal transfusion strategy and reduces exposure to blood products, multiple studies have shown that in practice, the hemoglobin threshold is higher than the evidence indicates, exposing additional children to the potential complications associated with RBC transfusion without any expectation of benefit (17–22). Multiple surveys and studies indicate that pediatric intensivists have only partially adopted a restrictive transfusion strategy (20–22). Furthermore, there remains a paucity of evidence to guide transfusion practice in critically ill children with hemodynamic instability. Guidelines for RBC transfusion practice in critically ill adults have been published (23), although the generalizability to critically ill children is uncertain. Pediatric RBC transfusion guidelines in 2004 have addressed RBC transfusion decision-making in children (24); however, despite additional data, there have been no recent consensus statements or guidelines evaluating the practice of RBC transfusion specifically in critically ill children despite emerging data.

The need to update guidance for RBC transfusion decision-making in critically ill children prompted the organization of the Pediatric Critical Care Transfusion and Anemia EXpertise Initiative (TAXI) through the Pediatric Critical Care Blood Research Network (BloodNet) and the Pediatric Acute Lung Injury and Investigators (PALISI) Network. The goals of the TAXI conference series were to bring together international, multidisciplinary experts to 1) to develop evidence-based and, when evidence is lacking, expert-based consensus statements to guide transfusion and blood management practices, with the first series focusing on RBC transfusion practices for those caring for critically ill children, 2) to create an implementation initiative in collaboration with implementation experts to develop specific strategies for adaptive dissemination and implementation into various clinical/research environments that would best ensure uptake, and 3) to develop future research priorities for study of RBC transfusion in critically ill children and foster international collaboration in pursuit of these goals.

METHODS

The methodology for TAXI was modeled after the Pediatric Acute Lung Injury Consensus Conference (PALICC) methodology (25) and followed the standards set by the Institute of Medicine for guideline development to create comprehensive evidence-based and, when evidence was lacking, expert based recommendations for RBC decision-making in critically ill children. TAXI was proposed to and fully endorsed by the Pediatric Critical Care BloodNet. The focus on RBCs represents the first of multiple planned consensus series focused on developing guidelines for transfusion (e.g., RBC, plasma, platelets) and blood management decision-making in critically ill children. The TAXI Executive Committee, composed of two TAXI cochairs, the BloodNet Executive Committee, and evidence-based medicine experts from the Johns Hopkins Evidence-Based Practice Center provided oversight of the entire TAXI process. The details of the TAXI methodology and expert selection are fully described in a supplement of *Pediatric Critical Care Medicine* (26).

Briefly, the TAXI process included systematic reviews and three consensus meetings, with substantial work between meetings, conducted over the course of 2 years, with an overview provided in **Figure 1**. Thirty-eight content experts and four nonvoting methodology and implementation experts, representing eight countries, 29 academic institutions, and eight medical specialties agreed and participated in all aspects of TAXI (Appendix 1).

During the first TAXI meeting, experts vetted and agreed upon the recommendation development methodology, common definitions, and the following nine clinical subtopics: indications for RBC transfusion based on hemoglobin and physiologic thresholds in critically ill children: 1) in the general PICU population, with 2) respiratory failure, 3) nonhemorrhagic shock, 4) nonlife-threatening bleeding and hemorrhagic shock, 5) acute brain injury, 6) acquired and congenital heart disease, 7) sickle cell and oncologic disease, 8) support from extracorporeal membrane oxygenation (ECMO), ventricular assist devices (VADs), renal replacement therapy (RRT), and 9) the use of alternative processing of blood products.

The experts agreed upon common definitions to apply to all subgroups reviews and recommendations, as follows: 1) "RBC transfusion"—any transfusion of RBC, whatever the volume or the type of blood product (RBC units or whole blood) transfused; 2) "critically ill children or those at risk for critical illness"—pediatric patients within a an ICU which admits full-term infants and any child up to at least 18 years old; 3) "hemodynamically stable"—mean arterial pressure is not less than 2 SDs below normal mean for age, and cardiovascular support (vasopressors/inotropes and fluids) has not been increased in the last 2 hours, as defined in the TRIPICU study (15); and 4) "severe pediatric acute respiratory distress syndrome"—as defined by PALICC (27).

We conducted systematic review for the nine subtopics and analyzed the evidence using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology and the GRADEPRO tool (McMaster University and Evidence Prime Inc., Hamilton, ON, Canada) and is described in detail (with tables for search terms number of articles included, etc.) in the TAXI methodology of a supplement of *Pediatric Critical Care Medicine* (26).

The recommendations and supporting arguments were drafted after completion of the systematic reviews, discussed in depth, and revised during the second expert meeting (Fig. 1). The strength, "strong" (level 1) or "weak" (level 2), was based on weighing the balance between benefits, risks, burden, and the costs, and the level of evidence, "high quality" or level A, "moderate-quality evidence" or level B and "low-quality evidence" or level C, was based on the certainty of the evidence. Recommendations without pediatric evidence were presented with justification and rationale by the subgroups for expert consensus. Using the Research and Development/UCLA Appropriateness Method (28), the recommendations were scored anonymously using an online tool (Survey Monkey, San Mateo, CA). Agreement was defined a priori as 80% of the experts rating the recommendation a 7, 8, or 9. Recommendations that did not achieve agreement were returned to the respective subgroup experts with the associated comments from the voting process for revision and subsequent rescoring. All recommendations met greater than 80% agreement after the second round of scoring. During the third expert meeting, the recommendations were presented and any changes made to the recommendations were rescored to confirm that the changes did not alter the intention of the recommendation. A total of three rounds of voting were performed.

Finally, TAXI was dedicated to formulating a TAXI decision tree, formalizing implementation goals and strategies

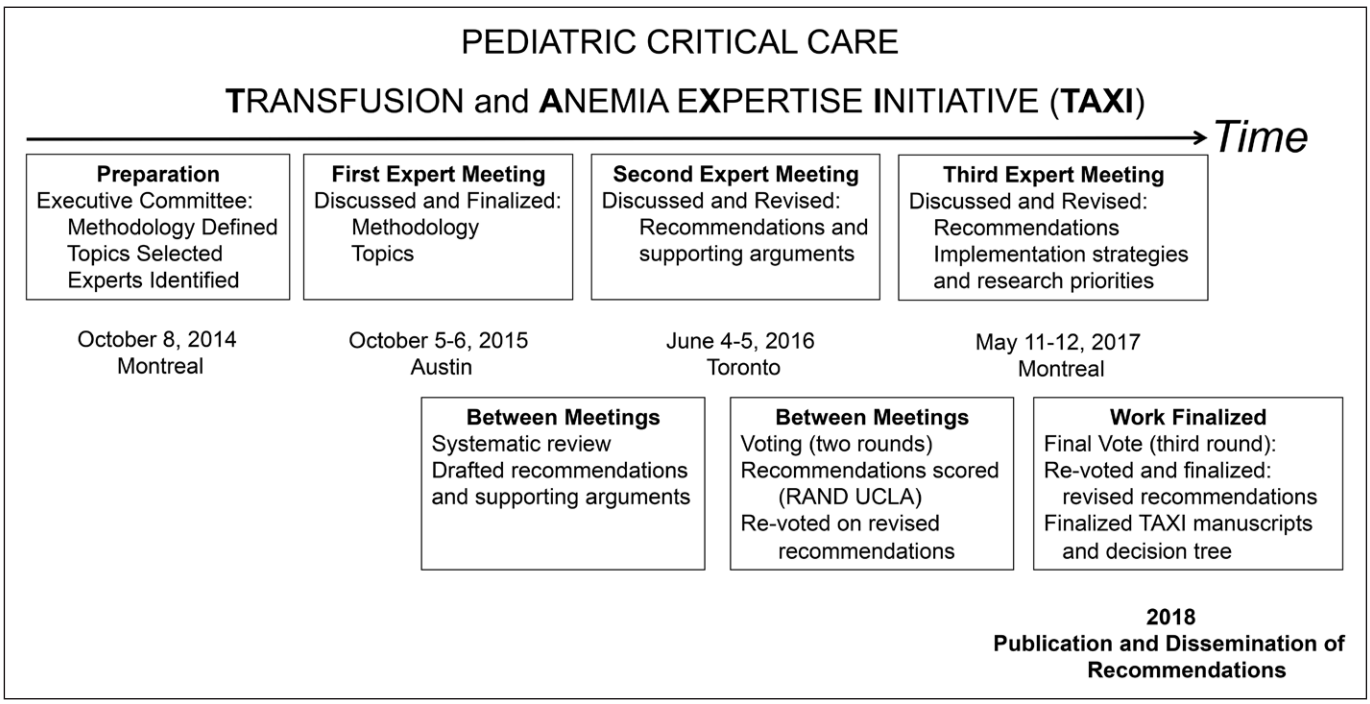

Figure 1. Timeline and overview of the Pediatric Critical Care Transfusion and Anemia Expertise Initiative (TAXI). RAND = Research And Development.

to best support uptake into the pediatric critical care and transfusion medicine communities (29), as well as discussing TAXI research priorities. During the third meeting, a full day was dedicated to discussion/development of both implementation strategies (30) and knowledge gaps in RBC transfusion decision-making to guide future research priorities.

RESULTS

The consensus recommendations of TAXI are presented below. All justifications, literature supporting the recommendations from the systematic review, as well as discussion of research priorities within the nine subgroups are presented in separate subgroup manuscripts in a supplement of *Pediatric Critical Care Medicine* (31–39). The subgroups developed, scored, and finalized 100 recommendations (55 specific clinical recommendations, and 45 research recommendations, which are presented separately, by subgroup) and two good practice statements, of which all met a priori greater than 80% agreement. Of the 119 recommendations initially developed, 95% ($n = 113$) met agreement after the first round, and the remaining 5% met agreement after the second round of voting. Nineteen recommendations were subsequently removed for redundancy. The level of evidence (GRADE) is provided for recommendations that are evidence based. Voting data (median and interquartile range [IQR]) are provided with each recommendation. Recommendations without direct pediatric evidence, but included based on strong expert opinion, are labeled as "consensus panel expertise." The TAXI experts placed value on avoiding the rare, but potentially, serious complications of RBC transfusion; therefore, when evidence suggested no harm from transfusion, a restrictive decision-making strategy was recommended. The RBC transfusion Good Practice Statements, created by the TAXI experts, apply to all critically ill patients, when deciding to transfuse an individual patient. The TAXI consensus recommendations will not apply to all individual transfusion decisions and are not intended to be an absolute standard for transfusion decision-making.

Good Practice Statements (31)

1. When deciding to transfuse an individual critically ill child, we recommend considering not only the hemoglobin concentration but also the overall clinical context (e.g., symptoms, signs, physiologic markers, laboratory results) and the risks, benefits, and alternatives to transfusion. *Consensus panel expertise, Voting Data (n = 29): 97% Agreement (n = 29), Median 9, IQR 9–9.*

2. In critically ill children or those at risk for critical illness, we recommend measuring a hemoglobin concentration before prescribing each RBC transfusion; knowledge of hemoglobin concentration is not required before RBC transfusion if the patient has life-threatening bleeding. *Consensus panel expertise, Voting Data (n = 35): 100% Agreement, Median 9, IQR 8–9.*

Indications for RBC Transfusion for the General Critically Ill Child Based on Hemoglobin and Physiologic Thresholds (31)

The following recommendations are focused on transfusion decision-making in the general critically ill child and "exclude" the eight specific subpopulations of critically ill children discussed further in this text.

1.1 In critically Ill children or those at risk for critical illness, we recommend a RBC transfusion if the hemoglobin concentration is less than 5 g/dL. *Strong recommendation, Low quality pediatric evidence (1C), 100% Agreement (n = 35), Median 9, IQR 8–9.*

1.2 In critically ill children or those at risk for critical illness, we cannot recommend a specific RBC transfusion decision-making strategy that is based upon physiologic metrics and biomarkers. *Consensus panel expertise, 91% Agreement (n = 35), Median 8, IQR 8–9.*

1.3 In critically ill children or those at risk for critical illness, who are hemodynamically stable and who have an hemoglobin concentration greater than or equal to 7 g/dL, we recommend not administering a RBC transfusion. *Strong recommendation, Moderate quality pediatric evidence (1B), 97% Agreement (n = 29), Median 9, IQR 8–9.*

1.4 In critically ill children with acute postoperative nonhemorrhagic anemia (excluding cardiac surgery), who are hemodynamically stable, we recommend not administering a RBC transfusion if the hemoglobin concentration is greater than or equal to 7 g/dL. *Weak recommendation, Low quality pediatric evidence (2C), 93% Agreement (n = 29), Median 8, IQR 8–9.*

1.5 There is insufficient evidence to make a recommendation regarding transfusion thresholds for critically ill children who have an hemoglobin concentration between 5 and 7 g/dL. However, it is reasonable to consider transfusion based on clinical judgment in these children. *Consensus panel expertise, 100% Agreement (n = 29), Median 9, IQR 9–9.*

1.6 In critically ill children or those at risk for critical illness who are hemodynamically stable, we recommend that the post-transfusion goal be to relieve the indication for transfusion and not necessarily achieve normal hemoglobin for age. A reasonable hemoglobin goal post transfusion is a range between 7.0 g/dL and 9.5 g/dL. *Weak recommendation, Low quality pediatric evidence (2C), 96% Agreement (n = 28), Median 8, IQR 8–9.*

Indications for RBC Transfusion for the Critically Ill Child With Respiratory Failure (32)

2.1 We recommend RBC transfusion for critically ill children with respiratory failure who have an hemoglobin concentration less than 5 g/dL. *Strong recommendation, Low quality pediatric evidence (1C), 100% Agreement (n = 35), Median 9, IQR 8–9.*

2.2 In critically ill children with respiratory failure who do not have severe acute hypoxemia, a chronic cyanotic condition, or hemolytic anemia, and whose hemodynamic status is stable, we recommend not administering a RBC transfusion if the hemoglobin concentration is greater than or equal to 7 g/dL.

Strong recommendation, Moderate quality pediatric evidence (1B), 100% Agreement (n = 29), Median 8.5, IQR 8–9.

2.3 In critically ill children with respiratory failure who have severe hypoxemia, we cannot make a recommendation regarding optimal RBC transfusion strategy. *Consensus panel expertise, 97% Agreement (n = 29), Median 8, IQR 8–9.*

2.4 There is insufficient evidence to make a recommendation regarding transfusion thresholds for critically ill children with respiratory failure who have an hemoglobin concentration between 5 and 7 g/dL. However, it is reasonable to consider transfusion based on clinical judgment in these children. *Consensus panel expertise, 97% Agreement (n = 35), Median 9, IQR 8–9.*

2.5 We cannot recommend a specific RBC transfusion decision-making strategy using physiologic-based metrics and biomarkers in critically children with respiratory failure. *Consensus panel expertise, 100% Agreement (n = 35), Median 8, IQR 8–9.*

Indications for RBC Transfusion for the Critically Ill Child With Nonhemorrhagic Shock (33)

3.1 In critically ill children with nonhemorrhagic shock, we recommend to consider all possible strategies to augment oxygen delivery and decrease oxygen demand and not RBC transfusion alone. *Consensus panel expertise, 97% Agreement (n = 35), 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 nonhemorrhagic shock. *Consensus panel expertise, 97% Agreement (n = 35), Median 8, IQR 8–9.*

3.3 We cannot make a recommendation regarding transfusion thresholds for critically ill children with unstable nonhemorrhagic shock. *Consensus panel expertise, 100% Agreement (n = 35), Median 9, IQR 8–9*

3.4 In hemodynamically stable critically ill children with a diagnosis of severe sepsis or septic shock, we recommend not administering a RBC transfusion if the hemoglobin concentration is greater than or equal to 7 g/dL. *Weak recommendation, Low quality pediatric evidence (2C), 96% Agreement (n = 29), Median 8, IQR 8–9.*

Indications for RBC Transfusion for the Critically Ill Child With Nonlife-Threatening Bleeding or Hemorrhagic Shock (34)

4.1 In critically ill children with nonlife-threatening bleeding, we recommend that a RBC transfusion should be given for an hemoglobin concentration less than 5 g/dL. *Weak recommendation, Low quality pediatric evidence (2C), 100% Agreement (n = 35), Median 9, IQR 8–9.*

4.2 In critically ill children with nonlife-threatening bleeding, we recommend that a RBC transfusion should be considered for an hemoglobin concentration between 5 and 7 g/dL. *Consensus panel expertise, 100% Agreement (n = 35), Median 9, IQR 8–9.*

4.3 In critically ill children with hemorrhagic shock, we suggest that RBCs, plasma, and platelets be transfused empirically in ratios between 2:1:1 to 1:1:1 for RBCs:plasma:platelets until the bleeding is no longer life-threatening. *Consensus panel expertise, 94% Agreement (n = 35), Median 9, IQR 8–9.*

Indications for RBC Transfusion for the Critically Ill Child With Acute Brain Injury (35)

5.1 In critically ill children with acute brain injury (e.g., trauma, stroke), a RBC transfusion could be considered if the hemoglobin concentration falls between 7 and 10 g/dL. *Consensus panel expertise, 90% Agreement (n = 30), Median 8, IQR 7–8.*

5.2 In critically ill children with acute brain injury (e.g., trauma, stroke), we cannot recommend the use of brain oxygen monitoring in determining when to administer a RBC transfusion. *Consensus panel expertise, 91% Agreement (n = 35), Median 8, IQR 8–8.*

Indications for RBC Transfusion for the Critically Ill Child With Acquired and Congenital Heart Disease (36)

Good Practice Statements. 6.1 In children with cardiac disease, we recommend optimization of all the components contributing to oxygen delivery, including but not limited to achievement/maintenance of normal sinus rhythm and/or heart rate control, optimal preload and contractility, optimal right ventricular and left ventricular afterload, adequate oxygenation, and/or reduction of oxygen demand, as appropriate before initiation of RBC transfusion, except in the case of hemorrhagic shock. *Consensus panel expertise, 94% Agreement (n = 35), Median 8, IQR 8–9.*

6.2 For all children with congenital and acquired heart disease, the benefits and risks of transfusion must be considered before transfusion. Whenever possible, adoption of blood sparing and conservation procedures and guidelines should be implemented. *Consensus panel expertise, 93% Agreement (n = 30), Median 8, IQR 8–9.*

6.3 In children undergoing cardiac surgery (repair or palliation) or heart transplants, when deciding to transfuse, we recommend considering not only the hemoglobin concentration but also the overall clinical context (e.g., symptoms, signs, physiologic markers, laboratory results) and the risk, benefits, and alternatives to transfusion. *Consensus panel expertise, 97% Agreement (n = 35), Median 8, IQR 8–9.*

6.4 In infants and children with congenital heart disease, we recommend investigating and treating preoperative anemia in addition to implementing transfusion/blood management guidelines/blood conservation practices. *Consensus panel expertise, 94% Agreement (n = 35), Median 9, IQR 8–9.*

6.5 In hemodynamically stable infants and children with congenital heart disease (CHD) and adequate oxygenation (for their cardiac lesion) and normal end organ function who are awaiting cardiac surgery, we recommend that the risks, benefits, and alternatives of RBC transfusions must be carefully considered when deciding to give an RBC transfusion. *Consensus panel expertise, 85% Agreement (n = 35), Median 8, IQR 7.25–9.*

Clinical Recommendations. 6.6 In children with documented right or left ventricular myocardial dysfunction (acquired or

congenital), there is insufficient evidence to support transfusion to target a specific hemoglobin concentration. Furthermore, there is no evidence that transfusion above an hemoglobin level greater than 10 g/dL is beneficial. *Consensus panel expertise, 83% Agreement (n = 30), Median 8, IQR 7.25–8.75.*

6.7 In children with structurally normal heart and idiopathic or acquired pulmonary hypertension (defined as a mean pulmonary arterial pressure > 25 mm Hg with normal pulmonary artery occlusion pressure), there is insufficient evidence to support transfusion to target a specific hemoglobin concentration. Furthermore, there is no evidence that transfusion above an hemoglobin level greater than 10 g/dL is beneficial. *Consensus panel expertise, 97% Agreement (n = 35), Median 9, IQR 8–9.*

6.8 In hemodynamically stable critically ill infants and children with uncorrected CHD, we recommend RBC transfusion to maintain an hemoglobin concentration of at least 7.0–9.0 g/dL depending on the degree of cardiopulmonary reserve. *Weak recommendation, Low quality pediatric evidence (2C), 81% Agreement (n = 35), Median 8, IQR 7–8.*

6.9 In infants and children undergoing cardiac surgery, we recommend development and adoption of intra- and postoperative blood sparing and blood conservation procedures and guidelines with the goal of reducing the number and volume of RBCs transfused (pump prime, on cardiopulmonary bypass [CPB], after separation from CPB, and postoperative) and limiting donor exposures and other blood component transfusions. *Strong recommendation, Low quality pediatric evidence (1C), 100% Agreement (n = 35), Median 9, IQR 8.*

6.10 In infants undergoing stage 1 palliation procedures (Norwood, Damus-Kaye-Stansel, Blalock-Taussig or central shunt, or pulmonary artery band) for single ventricle physiology who have stable hemodynamics and adequate oxygenation (for their cardiac lesion) and normal end-organ function, we recommend avoiding reflexive ("solely hemoglobin based") RBC transfusions if the hemoglobin concentration is greater than 9.0 g/dL. *Weak recommendation, Low quality pediatric evidence (2C) 96% Agreement (n = 29), Median 8, IQR 7–9.*

6.11 In hemodynamically stable infants and children with single ventricle physiology undergoing stages 2 and 3 procedures with adequate oxygen delivery, we recommend not administering a RBC transfusion if the hemoglobin concentration is greater than 9 g/dL. *Weak recommendation, Low quality pediatric evidence (2C), 96% Agreement (n = 29), Median 8, IQR 8–9.*

6.12 In infants and children with CHD undergoing biventricular repair who are hemodynamically stable and have adequate oxygenation and normal end-organ function, we recommend not administering a RBC transfusion if the hemoglobin concentration is greater than or equal to 7.0 g/dL. *Strong recommendation, Moderate quality pediatric evidence (1B), 100% Agreement (n = 29), Median 8.5, IQR 7–9.*

6.13 Standard issue RBC transfusions should be used in children with acquired or congenital heart disease as there are insufficient data supporting the transfusion of RBCs of shortened storage age in this population. *Weak recommendation, Low quality pediatric evidence (2C), 93% Agreement (n = 29), Median 8, IQR 8–9.*

Indications for RBC Transfusion for the Critically Ill Child With Hematologic and Oncologic Diagnoses (37)

Sickle Cell Disease. 7.1 In children with sickle cell disease who are critically ill or those at risk of critical illness, we recommend RBC transfusion to achieve a target hemoglobin concentration of 10 g/dL (rather than a hemoglobin S [HbS] of < 30%) prior to a surgical procedure requiring general anesthesia. *Strong recommendation, Moderate quality pediatric evidence (1B), 96% Agreement (n = 29), Median 8, IQR 8–9.*

7.2 In children with sickle cell disease who are critically ill or at risk of critical illness, there is insufficient evidence to recommend an optimal hemoglobin concentration threshold or percent HbS for RBC transfusion prior to minor surgical procedures. *Consensus panel expertise, 91% Agreement (n = 35), Median 8, IQR 8–9.*

7.3 In children with sickle cell disease and acute chest syndrome (ACS) who are critically ill, we recommend an exchange transfusion over a simple (nonexchange) transfusion if the child's condition is deteriorating (based on clinical judgment); otherwise, a simple (nonexchange) RBC transfusion is recommended. *Strong recommendation, Low quality pediatric evidence (1C), 97% Agreement (n = 35), Median 9, IQR 8–9.*

7.4 In children with sickle cell disease and pulmonary hypertension who are critically ill or at risk for critical illness, there is insufficient evidence to recommend the optimal hemoglobin concentration threshold or percent HbS for RBC transfusion or the method of RBC transfusion. *Consensus panel expertise, 97% Agreement (n = 35), Median 9, IQR 8–9.*

7.5 In children with sickle cell disease and acute stroke who are critically ill, there is insufficient evidence to recommend the optimal hemoglobin concentration threshold or percent HbS for RBC transfusion; the preferred method of RBC transfusion is exchange transfusion if instituted quickly. *Consensus panel expertise, 97% Agreement (n = 35), Median 9, IQR 8–9.*

Oncologic Disease. 7.6 In children with oncologic diagnoses who are critically ill or at risk for critical illness, and hemodynamically stable, we suggest an hemoglobin concentration of 7–8 g/dL be considered a threshold for RBC transfusion. *Weak recommendation, Low quality pediatric evidence (2C 88% Agreement (n = 35), Median 8, IQR 7–8.*

Bone Marrow Transplantation. 7.7 In children undergoing hematopoietic stem cell transplant (HSCT) who are critically ill or at risk for critical illness and are hemodynamically stable, we suggest a hemoglobin concentration of 7–8 g/dL be considered a threshold for RBC transfusion. *Weak recommendation, Low quality pediatric evidence (2C) 88% Agreement (n = 35), Median 8, IQR 7–8.*

Indications for RBC Transfusion for the Critically Ill Child Receiving Support From ECMO, VAD, and RRT (38)

ECMO. 8.1 In critically ill children on ECMO, we recommend reporting hemoglobin concentration, rather than hematocrit, for RBC transfusion threshold algorithms. *Consensus panel expertise 97% Agreement (n = 35), Median 8, IQR 8–9.*

8.2 In critically ill children on ECMO, we recommend measuring hemoglobin concentration before all RBC transfusion, unless the patient experiences life-threatening bleeding. *Consensus panel expertise. 97% Agreement (n = 35), Median 8, IQR 8–9.*

8.3 In critically ill children on ECMO, we recommend that adoption of blood sparing and conservation procedures and guidelines should be implemented. *Consensus panel expertise. Voting Data (n = 35): 94% Agreement, Median 8, IQR 8–9.*

8.4 In critically ill children on ECMO, we recommend taking measures to minimize the number of donor exposures. *Consensus panel expertise, 97% Agreement (n = 35), Median 8, IQR 8–9.*

8.5 In critically ill children on ECMO, we recommend that all RBC exposure within circuit prime be reported in pediatric ECMO transfusion studies and quality improvement projects. *Consensus panel expertise, 94% Agreement (n = 35), Median 8, IQR 8–9.*

8.6 In critically ill children on ECMO, we recommend using physiologic metrics and biomarkers of oxygen delivery in addition to hemoglobin concentration to guide RBC transfusion. Administration of a RBC transfusion should be based on evidence of inadequate cardiorespiratory support or decreased systemic and/or regional oxygen delivery. *Weak recommendation, Low quality pediatric evidence (2C), 97% Agreement (n = 35), Median 8, IQR 8–9.*

8.7 In critically ill children on ECMO, there is insufficient evidence to recommend a specific RBC transfusion decision-making strategy using physiologic-based metrics and biomarkers. *Consensus panel expertise, 97% Agreement (n = 35), Median 8, IQR 8–9.*

VAD. 8.8 In critically ill children on VAD support, we recommend using physiologic metrics and biomarkers of oxygen delivery in addition to hemoglobin concentration to guide RBC transfusion. Administration of a RBC transfusion should be based on evidence of inadequate cardiorespiratory support or decreased systemic and/or regional oxygen delivery. *Consensus panel expertise, 94% Agreement (n = 35), Median 8, IQR 8–9.*

RRT. 8.9 In critically ill children on RRT support, we recommend using the smallest circuit size that will provide adequate RRT while minimizing a driver for RBC transfusion specific to RRT (i.e., loss of blood volume that arises with circuit dysfunction/replacement of the circuit). *Consensus panel expertise, 100% Agreement (n = 35), Median 9, IQR 8–9.*

8.10 In critically ill children on RRT support who are hemodynamically stable with optimized intravascular volume status and no evidence of inadequate oxygen delivery or bleeding, we recommend not routinely administering a RBC transfusion if the hemoglobin concentration is greater than 7 g/dL. *Consensus panel expertise, 100% Agreement (n = 35), Median 8, IQR 8–9*

Selection and Processing of RBC Components in Critically Ill Children (39)

9.1 We recommend the use of irradiated cellular blood components for all critically ill children at risk for transfusion-associated graft versus host disease due to severe congenital or acquired causes of immune deficiency. *Consensus panel expertise, 97% Agreement (n = 35), Median 9, IQR 8–9.*

9.2 We recommend the use of irradiated cellular blood components for all critically ill children when the blood donor is a blood relative of the child. *Strong recommendation, Low quality pediatric evidence (1C), 100% Agreement (n = 35), Median 9, IQR 8–9.*

9.3 We recommend the use of the washed cellular blood components and avoidance of other plasma-containing products (e.g., plasma, cryoprecipitate, etc.) for critically ill children with history of severe allergic reactions or anaphylaxis to blood transfusions, although patient factors appear to be critically important in the pathogenesis. *Consensus panel expertise, 100% Agreement (n = 29), Median 9, IQR 8–9.*

9.4 For critically ill children with a history of severe allergic transfusion reaction(s), we recommend considering evaluation of allergic stigmata (antiimmunoglobulin A [IgA] antibodies in IgA-deficient individuals, antihaptoglobin antibodies—using a pretransfusion specimen) prior to RBC transfusion. *Consensus panel expertise, 96% Agreement (n = 29), Median 8, IQR 8–9.*

9.5 In critically ill children with suspected or documented severe IgA deficiency (undetectable), evidence of anti-IgA antibodies, and/or a history of a severe transfusion reaction, we recommend using IgA-deficient blood components obtained either from an IgA-deficient donor and/or washed cellular components. *Consensus panel expertise, 100% Agreement (n = 29), Median 8.5, IQR 8–9.*

TAXI Research Recommendations

Indications for RBC Transfusion for the General Critically Ill Child Based on Hemoglobin and Physiologic Thresholds (31).

R1.1 In critically ill children or those at risk for critical illness, we recommend creating clinical research programs specifically designed to determine the efficacy and safety of transfusion decision-making based upon physiologic metrics and biomarkers. *Consensus panel expertise, 100% Agreement (n = 35), Median 9, IQR 8–9.*

R1.2 In children with critical illness or at risk for critical illness, we recommend investigation that identifies and evaluates biomarkers and/or physiologic measures that characterize anemia intolerance. *Consensus panel expertise, 100% Agreement (n = 35), Median 9, IQR 8–9.*

R1.3 We recommend investigation to determine biomarkers or physiologic measures that identify anemia intolerance, defined as threat to oxygen delivery and/or oxygen consumption homeostasis, and manifested as an increase in global anaerobic metabolism. *Consensus panel expertise 97% Agreement (n = 35), Median 8, IQR 8–9.*

R1.4 We recommend investigation that identifies and evaluates biomarkers and/or physiologic metrics of anemia intolerance specific to individual vital organs, which may be present and indicate patient-specific likelihood of benefit from transfusion, even in the absence of measures indicating systemic impairment of oxygen delivery and/or oxygen consumption homeostasis. *Consensus panel expertise, 97% Agreement (n = 35), Median 9, IQR 8–9.*

R1.5 We recommend undertaking future studies aiming to identify the appropriate hemoglobin concentration to guide administration of a RBC transfusion in hemodynamically unstable critically ill children. *Consensus panel expertise, 91% Agreement (n = 35), Median 9, IQR 8–9.*

R1.6 We recommend undertaking future studies aiming to identify the appropriate hemoglobin concentration to guide administration of a RBC transfusion in subpopulations of hemodynamically stable critically ill children or those at risk for critical illness. *Consensus panel expertise, 91% Agreement (n = 35), Median 9, IQR 8–9.*

R1.7 We recommend undertaking future studies aiming to identify the appropriate hemoglobin concentration to guide administration of a RBC transfusion in hemodynamically stable critically ill children or those at risk for critical illness, when the hemoglobin level is between 5 and 7 g/dL. *Consensus panel expertise, 83% Agreement (n = 35), Median 8, IQR 7–8.*

R1.8 We recommend investigation that will inform priority (e.g., sequencing) of RBC transfusion relative to other interventions, which may either 1) improve anemia tolerance or 2) improve oxygen delivery homeostasis by supporting physiologic compensation for anemia. *Consensus panel expertise, 91% Agreement (n = 35), Median 8, IQR 8–9.*

R1.9 In addition to investigation of physiologic metrics and biomarkers likely to indicate patient-specific likelihood of benefit of transfusion in patients with anemia, we recommend investigation that seeks evidence of patient-specific likelihood of harm from transfusion (both acute and long term). *Consensus panel expertise, 91% Agreement (n = 35), Median 9, IQR 8–9.*

R1.10 We recommend investigations that seek evidence on thresholds or triggers that would tell practitioners that the risk/benefit ratio tolerating anemia is higher than the risk/benefit ratio of giving a RBC transfusion in critically ill children. *Consensus panel expertise, 94% Agreement (n = 35) Median 9, IQR 8–9.*

R1.11 We recommend investigation that seeks evidence that, once the decision to transfuse has been made, will inform a titrated approach to administering RBCs, to maintain the risk of transfusion as low as reasonably achievable, while monitoring for resolution of the original indication for transfusion. *Consensus panel expertise, 97% Agreement (n = 35), Median 9, IQR 8–9.*

Indications for RBC Transfusion for the Critically Ill Child With Respiratory Failure (32). R2.1 We recommend future studies to evaluate the utility of physiologic markers of oxygen consumption and oxygen delivery that can guide RBC transfusion decisions for critically ill children with respiratory failure. *Consensus panel expertise, 97% Agreement (n = 35), Median 9, IQR 8–9.*

R2.2 We recommend further studies to determine the risk, benefits and alternatives of transfusion in unstable anemic children with respiratory failure, in particular if associated with severe hypoxemia or hemodynamic instability. *Consensus panel expertise, 100% Agreement (n = 35), Median 9, IQR 8–9*

Indications for RBC Transfusion for the Critically Ill Child With Nonhemorrhagic Shock (33). 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 nonhemorrhagic shock. *Consensus panel expertise, 97% Agreement (n = 35), Median 9, IQR 8–9.*

R3.2 We recommend future studies to determine optimum transfusion thresholds for critically ill children with nonhemorrhagic shock undergoing acute resuscitation. *Consensus panel expertise, 97% Agreement (n = 35), 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 nonhemorrhagic shock. *Consensus panel expertise, 97% Agreement (n = 35), Median 9, IQR 8–9.*

R3.4 We recommend future studies to determine long-term effects of anemia in children with nonhemorrhagic shock. *Consensus panel expertise, 100% Agreement (n = 35), Median 9, IQR 8–9.*

Indications for RBC Transfusion for the Critically Ill Child With Nonlife-Threatening and Hemorrhagic Shock (34). R4.1 In children with nonlife-threatening bleeding, we recommend future studies to develop physiologic and laboratory measures to indicate the need for RBC transfusions. *Consensus panel expertise, 94% Agreement (n = 35), Median 8, IQR 8–9.*

R4.2 We recommend future studies to determine if goal-directed hemostatic resuscitation improves survival compared with an empiric ratio approach in critically ill children with hemorrhagic shock. *Consensus panel expertise, 97% Agreement (n = 35), Median 8, IQR 8–9.*

R4.3 We recommend future studies to determine if low titer group O whole blood is more efficacious and safe compared with reconstituted whole blood with components for critically ill children with hemorrhagic shock. *Consensus panel expertise, 97% Agreement (n = 35), Median 8, IQR 8–9.*

Indications for RBC Transfusion for the Critically Ill Child With Acute Brain Injury (35). R5.1 In critically ill children with acute brain injury (e.g., trauma, stroke), we recommend further clinical trials testing the transfusion threshold or hemoglobin concentration that has the best long-term functional outcomes. In particular, specific populations need to be studied separately (e.g., trauma, stroke) since the physiology of oxygen delivery and extraction may differ. *Consensus panel expertise, 97% Agreement (n = 35), Median 9, IQR 8–9.*

R5.2 In critically ill children with acute brain injury (e.g., trauma, stroke), we recommend further clinical physiology studies to evaluate whether there is a role for brain oxygen monitoring in informing the decision whether to transfuse RBCs. *Consensus panel expertise, 94% Agreement (n = 35), Median 9, IQR 8–9.*

Indications for RBC Transfusion for the Critically Ill Child With Acquired and Congenital Heart Disease (36). R6.1 We recommend further studies to determine the risks and benefits of RBC transfusion in critically ill children with documented right or left ventricular myocardial dysfunction (acquired or congenital). *Consensus panel expertise, 97% Agreement (n = 35), Median 9, IQR 8–9.*

R6.2 We recommend further studies to determine the risks and benefits of transfusion in critically ill children with structurally normal hearts and idiopathic or acquired pulmonary hypertension (defined as a mean pulmonary arterial pressure > 25 mm Hg with normal pulmonary artery occlusion pressure). *Consensus panel expertise, 97% Agreement (n = 35), Median 9, IQR 8–9.*

R6.3 We recommend further studies in infants and children with CHD undergoing cardiac surgery to determine the impact of preoperative anemia management on perioperative RBC transfusions and outcomes. *Consensus panel expertise, 97% Agreement (n = 35), Median 9, IQR 8–9.*

R6.4 In infants and children undergoing cardiac surgery with CPB, further research is needed to determine the benefits and risks associated with the administration of RBC to the CPB prime, on-bypass and after separation of CPB. *Consensus panel expertise, 97% Agreement (n = 35), Median 8, IQR 8–9.*

R6.5 In infants and children undergoing cardiac surgery, further studies are needed to investigate the complex relationship between anemia, RBC transfusion, oxygen delivery, and utilization and outcomes, with focus on which patient subgroups may benefit from or be harmed by RBC transfusion. *Consensus panel expertise, 100% Agreement (n = 35), Median 9, IQR 8–9.*

R6.6 We recommend that clinical trials on RBC transfusion in pediatric cardiac surgery report the volume of RBC transfused and number of donor exposures. *Consensus panel expertise, 94% Agreement (n = 35), Median 9, IQR 8–9.*

R6.7 Further studies are needed in infants undergoing stage 1 surgical palliations for single ventricle physiology on hemoglobin concentration and physiologic indications for RBC transfusion. *Consensus panel expertise, 100% Agreement (n = 35), Median 9, IQR 8–9.*

R6.8 In children with acquired heart disease or CHD, further studies are warranted to determine if RBC storage time impacts clinical outcomes. *Weak recommendation, Low quality pediatric evidence (2C), 90% Agreement (n = 30), Median 8, IQR 8–9.*

Indications for RBC Transfusion for the Critically Ill Child With Hematologic and Oncologic Diagnoses (37)

Thalassemia. R7.1 In critically ill children with thalassemia, we recommend undertaking well-designed registries or expanding current initiatives to determine measures and limits of anemia tolerance, examine current practice, and define clinical outcomes to inform future research investigating the risks, benefits, and alternatives of RBC transfusion practice. *Consensus panel expertise, 100% Agreement (n = 29), Median 9, IQR 8–9.*

Sickle cell disease. R7.2 In children with sickle cell disease who are critically ill or at risk for critical illness, we recommend a well-designed registry or enhancement of existing network databases to further clarify optimal transfusion management. *Consensus panel expertise, 97% Agreement (n = 35), Median 9, IQR 8–9.*

R7.3 In children with sickle cell disease who are critically ill or at risk for critical illness, we recommend future research studies to evaluate the optimal hemoglobin concentration threshold and/or percent HbS to guide RBC transfusion decisions prior to minor surgical procedures. *Consensus panel expertise, (n = 35): 100% Agreement (n = 35), Median 9, IQR 8–9.*

Auto- or alloimmune hemolytic anemia. R7.4 In children with auto- and/or alloimmune–mediated hemolytic anemia who are critically ill or at risk for critical illness, we recommend undertaking well-designed registries to determine measures and limits of anemia tolerance, examine current practice, and define clinical outcomes to inform future research investigating the risks, benefits and alternatives of RBC transfusion practice. *Consensus panel expertise, 100% Agreement (n = 29), Median 9, IQR 8–9.*

Oncologic disease. R7.5 In children with oncologic disease who are critically ill or at risk of critical illness, we recommend undertaking well-designed registries or expanding current initiatives to inform future research investigating the risks, benefits, and alternatives of transfusion practice. *Consensus panel expertise, 97% Agreement (n = 29), Median 9, IQR 8–9.*

Radiation therapy. R7.6 In children receiving emergency radiation therapy who are critically ill or at risk for critical illness, we recommend exploration of existing databases to investigate the impact of hemoglobin concentration and RBC transfusion on disease response, survival, and other toxicities to inform creation of contemporary registries to investigate these associations. *Consensus panel expertise, 94% Agreement (n = 35), Median 8, IQR 8–9.*

Bone marrow transplantation. R7.7 In children undergoing HSCT who are critically ill or at risk for critical illness, we recommend undertaking well-designed registries or expanding current initiatives to inform future research investigating the risks, benefits, and alternatives of transfusion practice. *Consensus panel expertise, 97% Agreement (n = 29), Median 9, IQR 8–9.*

Indications for RBC Transfusion for the Critically Ill Child Receiving Support From ECMO, VAD, and RRT (38)

ECMO. R8.1 In critically ill children on ECMO, we recommend that hemoglobin concentrations and correlations with physiologic indications for RBC transfusion be studied to determine minimum thresholds for safety and efficacy of RBC transfusion. *Consensus panel expertise, 97% Agreement (n = 35), Median 9, IQR 8–9.*

R8.2 In critically ill children on ECMO, we recommend undertaking future studies of oxygen delivery/consumption markers (e.g., mixed venous saturation, cerebral oximetry, somatic oximetry, etc) in patients maintained at different hemoglobin thresholds. Such studies will aim to determine the optimal physiologic thresholds for RBC transfusion during pediatric ECMO. *Consensus panel expertise, 91% Agreement (n = 35), Median 9, IQR 8–9.*

R8.3 In critically ill children who suffer from cardiac arrest pre ECMO (i.e., extracorporeal cardiopulmonary resuscitation) and critically ill children with acute neurologic injury during ECMO (e.g., embolic stroke, intracranial hemorrhage, etc), we recommend undertaking future studies for

RBC transfusion strategies that optimize neuroprotection and recovery. *Consensus panel expertise, 91% Agreement (n = 35), Median 8, IQR 8–9.*

R8.4 In critically ill children on ECMO, we recommend undertaking future studies of the types of RBC manipulations and attributes and their impact on outcomes (e.g., storage duration, irradiation, leukoreduction, filtration, matching for Epstein–Barr Virus (EBV)/cytomegalovirus (CMV) serologic status, extended minor antigen matching, washing, etc). *Consensus panel expertise, 94% Agreement (n = 35), Median 8, IQR 8–9.*

VAD. R8.5 In critically ill children on VAD support, we recommend undertaking future studies of oxygen delivery/consumption markers (e.g., mixed venous saturation, cerebral oximetry, somatic oximetry, etc). Such studies will aim to determine the optimal physiologic thresholds for RBC transfusion during pediatric VAD support. *Consensus panel expertise, 100% Agreement (n = 35), Median 8.5, IQR 8–9.*

R8.6 In critically ill children on VAD/ECMO support, we recommend undertaking future studies to determine the impact of RBC transfusions on allosensitization, success of organ acquisition, and/or risk of rejection. *Consensus panel expertise, 100% Agreement (n = 35), Median 8, IQR 8–9.*

R8.7 In critically ill children on VAD support, we recommend undertaking future studies of the types of RBC manipulations and attributes and their impact on outcomes (e.g., storage duration, irradiation, leukoreduction, filtration, matching for CMV/EBV serologic status, extended minor antigen matching, washing, etc). *Consensus panel expertise, 100% Agreement (n = 35), Median 8, IQR 8–9.*

RRT. R8.8 In critically ill children on RRT support, we recommend undertaking future studies to determine how to optimize RRT length of use and hence minimize blood loss due to RRT circuit change/replacement. *Consensus panel expertise, 100% Agreement (n = 35), Median 8, IQR 8–9.*

DISCUSSION

The breadth of recommendations presented in this article aims to provide a comprehensive guide to RBC transfusion in a wide range of pediatric patients cared for in PICUs across the world. The goal of TAXI was to focus on the various subpopulations of children who have the highest risk of becoming anemic and receiving the most transfusions. TAXI used our best means of providing clear transfusion decision-making tools for PICU practitioners. The results of this effort have led to a combination of general guidance good practice statements, specific clinical recommendations backed by pediatric evidence, and a keen awareness of many areas still in need of evidence before any recommendation can be made.

The good practice statements are general principles that should apply to all clinical scenarios when a transfusion is being considered. Hemoglobin concentration can only be considered a surrogate marker of the capacity for oxygen delivery in critically ill children, so using it alone to determine RBC transfusion must be cautioned. The degree of compensation for anemia or anemia tolerance for critically ill patients through physiologic metrics should factor into decision-making. The need for thoughtful consideration of the risks and benefits of RBC transfusion has become increasingly necessary, as the untoward effects of RBC transfusions, such as NISHOT, have emerged, particularly in the critically ill (10–14). The limitations of donor RBC's to improve oxygen delivery deficits in the critically ill have also become more apparent (40); hence, the recommendation to enhance all other means of improving oxygen delivery or decreasing oxygen demand prior to RBC transfusion. These good practice statements all seek to highlight a major tenet of patient blood management principles: avoid unnecessary RBC transfusions (41).

The clinical recommendations supported by pediatric evidence are presented across the various subgroups. The decision tree, displayed in **Figure 2**, summarizes these specific recommendations. It is important to highlight that only studies conducted in children were used to support our recommendations. That limited our data significantly, as much more adult data are available, but also strengthened our conclusions for children. Important data on RBC transfusions in critically ill children exist and provide high GRADE evidence that "restrictive" RBC transfusion practices in certain populations are safe and tolerated and decrease RBC transfusion events and volume.

Using hemoglobin values to inform RBC transfusion decision-making remains the most common factor for pediatric intensivists (1) and has been the focus of most research on the topic. A hemoglobin concentration less than 5 g/dL should always be seen as a threshold for RBC transfusion (except in the case of auto- or alloimmune hemolytic anemia) due to increased mortality noted in children with such a low hemoglobin (2–6). When the hemoglobin level falls between 5.0 and 7.0 g/dL, it is unclear if the benefits outweigh the risks of RBC transfusion, necessitating further study. If the hemoglobin concentration is equal to or above 7 g/dL and the patient is hemodynamically stable, then there are few situations where a transfusion is recommended (15, 16, 31–34). In fact, our recommendations state to "not" transfuse children if the hemoglobin is that high. Those few situations where a higher hemoglobin may be preferred, such as single ventricle physiology, sickle cell disease with ACS, oncology or HSCT patients, hemorrhagic and nonhemorrhagic shock, and acute brain injury, are highlighted above. These recommendations can be considered an adoption of a broad based restrictive RBC transfusion approach, also in line with the principles of patient blood management.

The TAXI recommendations have many similarities to those published in adults (47). Restrictive transfusion practices were first studied and found safe in critically ill adults (35) and has led to multiple large-scale adult studies solidifying the practice of lower hemoglobin thresholds prior to RBC transfusion (36). Due to the inability to practically repeat many such studies in children, it is reassuring that the available pediatric data confirm and corroborate the adult findings. Subgroups incorporated adult data into their long text recommendation justification to provide a framework of available information. When stated, some adult data were used to inform expert consensus, if pediatric data were not available.

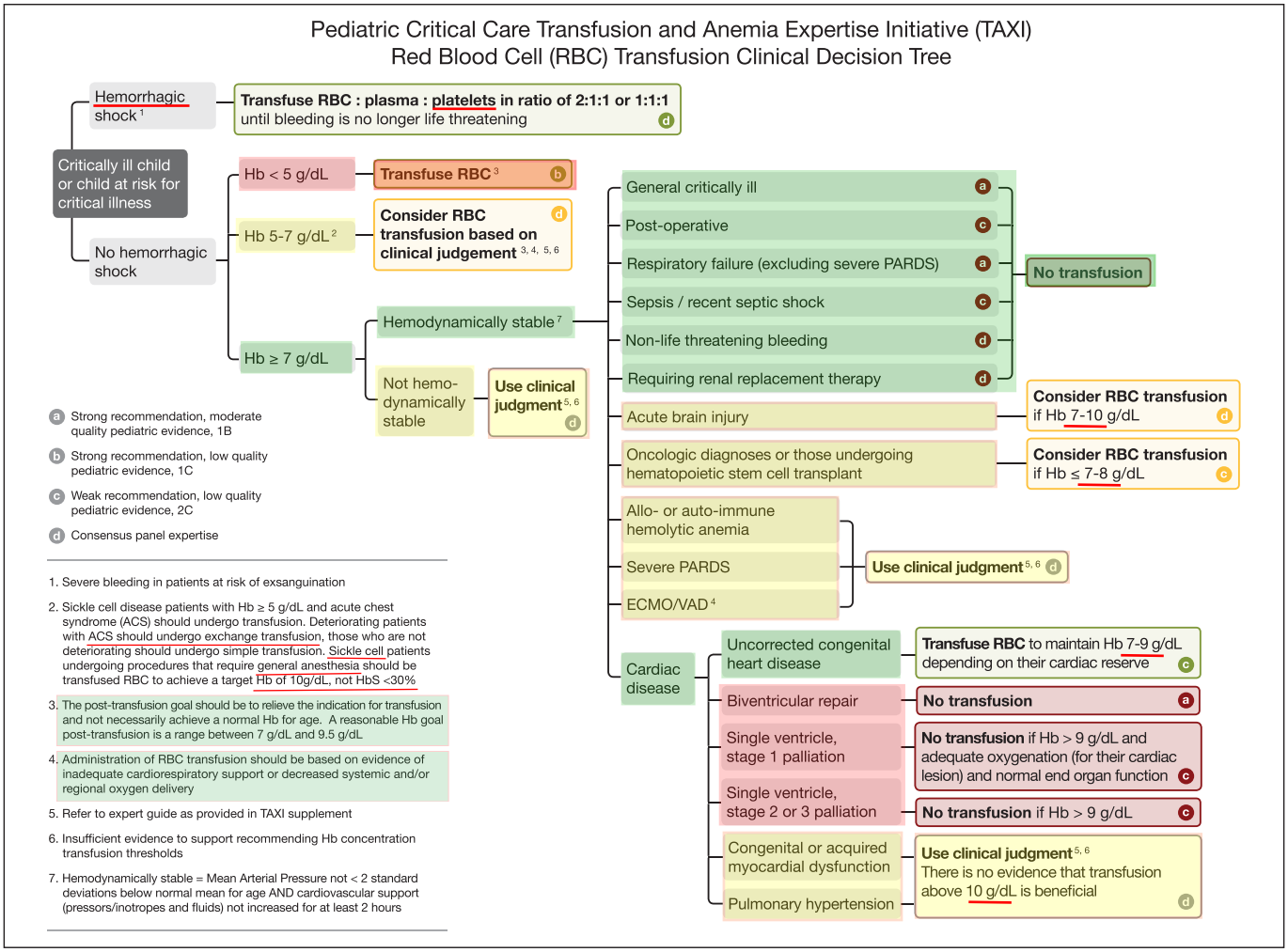

Figure 2. Transfusion and Anemia Expertise Initiative (TAXI) RBC transfusion decision tree for critically ill children. ACS = acute chest syndrome, ECMO = extracorporeal membrane oxygenation, Hb = hemoglobin, HbS = Hb S, PARDS = pediatric acute respiratory distress syndrome, VAD = ventricular assist device.

Our decision tree outlining the major recommendations of TAXI provides the first step in translating our recommendations into usable tools to improve uptake at the bedside. The TAXI implementation experts provided ongoing support, editing, and guidance on recommendation development (30, 48–50). We were thoughtful about dissemination of these recommendations, our target audience (primarily critical care practitioners, blood bankers), and publication strategy. The support of a broad range of organizations, such as BloodNet, PALISI, Society of Critical Care Medicine, Society for the Advancement of Blood Management (SABM), National Institute of Child Health and Human Development and National Heart, Lung, and Blood Institute (NHLBI), ensure that our recommendations will be broadly accepted and adopted. We plan to continue to update the recommendations using our online repository of published literature as new data emerge. Important research continues to be conducted on this topic and will need to be integrated on an ongoing basis.

As can be noted from our recommendations, almost half are considered research. This was deliberate to: 1) highlight what is not known in children and 2) galvanize the research community to help answer these important RBC transfusion questions. A major theme of our research recommendations is an emphasis on anemia tolerance in children and finding other means of RBC transfusion indication besides hemoglobin. Other physiologic metrics easily obtainable from children need to be studied to help guide RBC transfusions decisions, as well as to allow following the amelioration of these indications after transfusion. We are aware of the difficulties of conducting clinical trials in critically ill children but feel that we must encourage primary pediatric data to guide future recommendations. The funding priorities for research in RBC transfusions can hopefully be aligned with these recommendations. It is encouraging to see the research focus complement other efforts in pediatrics, such as the NHLBI state of the science initiative (51).

The strengths of TAXI are that it is the first consensus series to convene a group of international and multidisciplinary experts to use standardized guideline development principles to develop recommendations on RBC transfusion in critically ill children. It was a rigorous, large-scale, formal systematic review with expert consensus achieved through multiple rounds of debate and refinement. Agreement of over 80% of our experts allows

the recommendations to be highly acceptable to the pediatric critical care community. We engaged expertise from evidence-based and implementation science specialists to ensure that our systematic review of the literature and recommendation formation were performed according to published standards.

The TAXI recommendations are limited by the paucity of pediatric data in many subpopulations. There was heavy reliance on a few seminal articles that were applicable across multiple subpopulations. Other aspects of RBC transfusion, such as storage age of blood, volume of RBC to transfuse, whole blood factors, or RBC transfusion in active resuscitation, could not be addressed. Expert consensus for clinical recommendations must always be appropriately scrutinized for legitimacy. Our systematic approach, standardized procedures, and careful objective guidance of TAXI participants provide reassurance and validity to the final product. Study design for answering some of the research recommendations could be a significant challenge. TAXI's effort on RBC's alone was also deliberate to allow for a focused approach to our recommendations. Similar efforts are needed in other blood products, such as platelets or plasma. TAXI's RBC initiative is considered phase 1 of a comprehensive blood management program through BloodNet that will seek in the near future to engage experts in these other blood products to guide their use in children.

CONCLUSIONS

The TAXI Consensus Conference recommendations have the potential to impact global RBC transfusion practices for critically ill children. TAXI has developed pediatric specific recommendations regarding RBC transfusion management in the critically ill child across a variety of patient subpopulation, as well as recommendations to help guide future research priorities. Clinical recommendations emphasized relevant hemoglobin thresholds, and research recommendations emphasized a need for further understanding of anemia tolerance, physiologic thresholds, alternatives to RBC transfusion, and hemoglobin thresholds in populations with no pediatric literature. TAXI plans to continue to improve transfusion practices and ultimately outcomes in critically ill children receiving or at risk to receive an RBC transfusion by continuing to update its recommendations as new data emerge.

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APPENDIX 1: PEDIATRIC CRITICAL CARE TRANSFUSION AND ANEMIA EXPERTISE INITIATIVE (TAXI) MEMBERS

(* for executive committee) cochairs: Stacey L. Valentine, MD, MPH* and Scot T. Bateman, MD*, University of Massachusetts, Worcester, MA; Content experts: Section 1. General pediatric critical care patient based on physiologic and hemoglobin thresholds: Andrew Argent, MD, MBBCh, University of Cape Town, Cape Town, South Africa, Jeffrey L. Carson, MD, Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ, Jill M. Cholette, MD*, University of Rochester, Rochester, NY, Allan Doctor, MD*, Washington University of St. Louis, St. Louis, MO, Jacques Lacroix, MD*, Universite de Montréal, Montréal, QC, Canada, Kenneth Remy, MD, Washington University of St. Louis, St. Louis, MO; Section 2. Respiratory failure: Pierre Demaret, MD, MSc, CHC Liege, Liege, Belgium, Guillaume Emeriaud, MD, PhD, Universite de Montréal, Montréal, QC, Canada, Nabil E. Hassan, MD, University of Illinois, Champaign, IL, Martin C. J. Kneyber, MD, PhD, University of Groningen, Groningen, The Netherlands, Marisa Tucci, MD*, Universite de Montréal, Montréal, QC, Canada; Section 3. Shock, excluding hemorrhagic shock: Nina Guzzetta, MD, Emory University, Atlanta, GA, Mark W. Hall, MD, Ohio State University, Columbus, OH, Jennifer A. Muszynski, MD, MPH, Ohio State University, Columbus, OH, Philip C. Spinella, MD, Washington University of St. Louis, St. Louis, MO, Duncan Macrae, MBChB, Imperial College London, London United Kingdom; Section 4. Hemorrhagic shock and nonlife-threatening bleeding, Oliver Karam, MD, PhD, Virginia Commonwealth University, Richmond, VA, Robert T. Russell, MD, MPH, University of Alabama, Tuscaloosa, AL, Philip C. Spinella, MD*, Washington University of St. Louis, St. Louis, MO, Paul Stricker, MD, University of Pennsylvania, Philadelphia, PA, Adam M. Vogel, MD, Texas Children's Hospital, Houston, TX; Section 5. Acute brain injury: Philip C. Spinella, MD*, Washington University of St. Louis, St. Louis, MO, Robert C. Tasker, MA, MD, MBBS, Harvard University, Cambridge, MA, Alexis F. Turgeon, MD, MSc, Université Laval, Quebec, QC, Canada; Section 6. Acquired or congenital heart disease, Jill M. Cholette, MD*, University of Rochester, Rochester, NY, Steven M. Schwartz, MD, University of Toronto, Toronto, ON, Canada, Ariane Willems, MD, University of Brussels, Brussels, Belgium; Section 7. Sickle cell/ oncologic disease, Cassandra D. Josephson, MD, Emory University, Atlanta, GA, Naomi L. C. Luban, MD, George Washington University, Washington, DC, Leslie E. Lehmann, MD, Harvard University, Cambridge, MA, Robert I. Parker, MD*, Stony Brook University, Stony Brook, NY, Simon J. Stanworth, MD, NHS Blood and Transplant, Oxford, United Kingdom, Marie E. Steiner, MD, MS*, University of Minnesota, Minneapolis, MN, Nicole D. Zantek, MD, PhD, University of Minnesota, Minneapolis, MN, Section 8. Receiving support from extracorporeal, ventricular assist and renal replacement therapy devices: Melania M. Bembea, MD, PhD*, Johns Hopkins University, Baltimore, MD, Timothy Bunchman, MD, Virginia Commonwealth University, Richmond, VA, Ira M. Cheifetz, MD, Duke University, Durham, NC, James D. Fortenberry, MD, Emory University, Atlanta, GA, Marie E. Steiner, MD, MS*, University of Minnesota, Minneapolis, MN; Section 9. Selection and processing of RBC components: Meghan Delaney, DO, MPH, Children's National Health System, Washington, DC, Cassandra D. Josephson, MD, Emory University, Atlanta, GA, Robert I. Parker, MD*, Stony Brook University, Stony Brook, NY, Leo van de Watering, MD, Leiden University, Leiden, The Netherlands, Nicole D. Zantek, MD, PhD, University of Minnesota, Minneapolis, MN, evidenced-based medicine: Karen A. Robinson, PhD, Johns Hopkins University, Baltimore, MD, Melania M. Bembea, MD, PhD*, Johns Hopkins University, Baltimore, MD, implementation science: Sara Malone, MS, Washington University of St. Louis, St. Louis, MO, Katherine Steffen, MD, Stanford University, Stanford, CA.