Published in final edited form as:

Pediatr Crit Care Med. 2018 September ; 19(9) : S133–S136. doi:10.1097/PCC.0000000000001589.

Recommendations for Red Blood Cell Transfusion in Critically Ill Children with Acute Brain Injury from the Pediatric Critical Care Transfusion and Anemia Expertise Initiative

Robert C Tasker, MA, MBBS, MD, FRCP^{1,2}, Alexis F Turgeon, MD, MSc, FRCPC³, and Philip C Spinella, MD, FCCM⁴ for the Pediatric Critical Care Transfusion and Anemia Expertise Initiative (TAXI)*, in collaboration with Pediatric Critical Care Blood Research Network (BloodNet), and the Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network

¹Department of Neurology, Division of Critical Care Medicine, Harvard Medical School, Boston Children's Hospital, Boston, MA

²Department of Anesthesia (Pediatrics), Division of Critical Care Medicine, Harvard Medical School, Boston Children's Hospital, Boston, MA

³Department of Anesthesiology and Critical Care Medicine, Division of Critical Care Medicine, and CHU de Québec – Université Laval Research Center (Population Health and Optimal Health Practices Research Unit), Université Laval, Québec City, QC, Canada

⁴Department of Pediatrics, Division of Critical Care, Washington University in St Louis, St Louis, MO

Abstract

Objective—To present the recommendations and supporting literature for red blood cell (RBC) transfusions in critically ill children with acute brain injury 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 acute brain injury subgroup included three 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: Robert Tasker, MBBS, MD, Department of Anesthesiology, Division of Critical Care Medicine, Boston Children's Hospital, 300 Longwood Ave. Bader 621, Boston, MA 02115, 617-355-3508 (phone), 617-730-0453 (fax), Robert.tasker@childrens.harvard.edu.

*TAXI Members listed in Appendix 1

Copyright form disclosure: Dr. Spinella received funding from New Health Sciences. The remaining authors have disclosed that they do not have any potential conflicts of interest.

Results—TAXI Consensus Conference experts developed and agreed upon 2 clinical and 2 research recommendations focused on RBC transfusion in the critically ill child with acute brain injury. Recommendations include: consideration of RBC transfusion for a hemoglobin (Hb) concentration between 7–10 g/dL in patients with acute brain injury, and do not support the use of brain tissue partial pressure of oxygen monitoring to guide RBC transfusion decisions. Research is needed to better understand transfusion thresholds and brain tissue monitoring for pediatric patients with acute brain injury.

Conclusions—The TAXI Consensus Conference developed pediatric-specific clinical and research recommendations regarding RBC transfusion in the critically ill child with acute brain injury. While agreement among experts was very strong, the available pediatric evidence was extremely limited with major gaps in the literature.

Keywords

transfusion; blood; red blood cell; consensus conference; critically ill child; acute brain injury; traumatic brain injury; stroke

Introduction

Critically ill children with acute brain injury (ABI) include mainly those patients resuscitated after severe traumatic brain injury (sTBI) or following cerebrovascular stroke in the pediatric intensive care unit (PICU). In such instances, one aspect of clinical practice is the emphasis on cerebral perfusion and the adequacy of oxygen delivery to brain tissue. In this context RBC transfusion would theoretically increase oxygen content within the central circulation, although the effect on microvascular brain oxygen delivery is unknown. In addition, RBCs transfusions may have adverse effects due to the well described storage lesions (1). Therefore, it is unknown whether RBC transfusion is beneficial or detrimental to compromised brain tissue. Interventions to increase brain tissue partial pressure of oxygen (PbO₂) include raising the fractional inspired oxygen level, raising mean arterial pressure with vasopressors to improve cerebral perfusion pressure, and optimizing blood hemoglobin concentration (Hb). The following article reviews the current literature and details clinical and research recommendations for RBC transfusion in critically ill children with ABI.

Methods

The details of the methodology are described elsewhere in this supplement of *Pediatric Critical Care Medicine* (2). 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 acute brain injury 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. Three experts coordinated the ABI 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 ABI were divided into two categories: clinical recommendations, and research recommendations.

Results

The structured literature search identified 905 citations, of which 90 were selected for full text review. None of the reports yielded results related to the care of pediatric patients or met the criteria for inclusion in the final data analysis for pediatric recommendations. However, in the case of pediatric sTBI, nine case series were also identified that described a management protocol that included the use of a Hb target, some in the context of optimizing PbO_2 during treatment of raised intracranial pressure (ICP) (3–11). Since none of these studies examined a relationship between Hb and any outcome, but merely described that a specific Hb was used in practice, we could not include these data in our summative analysis. That said, it is of note that the thresholds used for transfusion varied and included Hb thresholds of 7.0 g/dL (hematocrit 21%) (11), 9.0 g/dL (10), 10.0 g/dL (hematocrit 30%) (3, 7), 11.0 g/dL (4), and 12.0 g/dL (5). The most recent of these reports come from 2012 (10) and 2016 (11).

Last, two systematic reviews of the ABI literature in adults were reviewed for comparative evidence (12, 13). In neurocritically ill adults there was no significant evidence to confirm or refute a difference in effect between lower- and higher-Hb groups, i.e., 7.0 to 10.0 g/dL versus 9.5 to 11.5 g/dL (12). In sTBI, RBC transfusion is frequent, and the thresholds for transfusion threshold practices varied widely between studies (i.e., 6 to 10 g/dL) with no evidence of benefit or harm (13).

Therefore, taking all of the above information together, two clinical recommendations and two research recommendations were developed by the experts and voted on. All recommendations reached agreement (>80%).

CLINICAL RECOMMENDATIONS

Recommendations

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

Rationale

In the absence of data to inform the recommendation for RBC transfusion, the TAXI experts took into consideration a number of factors in its determination. The evolution in pediatric sTBI management protocols was critical in formulating these recommendations, with the modern tendency to use 7.0 g/dL as the lowest Hb threshold for transfusion (11), and the evidence from systematic reviews in adults with ABI or sTBI (12, 13). When taken together, the most parsimonious conclusion was that a pediatric patient with ABI should receive RBC

transfusion when Hb <7.0 g/dL, but not when Hb >10.0 g/dL. There was no evidence to support a definitive recommendation to give a RBC transfusion when the Hb <7.0 g/dL in this population, as the only high quality randomized controlled trial on thresholds in pediatric intensive care units was not designed to study the benefit or harm of a restrictive transfusion strategy in pediatric ABI patients (14). In the range 7.0 to 10.0 g/dL, the consensus amongst all TAXI experts is that RBC transfusion can be considered.

5.2—In critically ill children with ABI (e.g., sTBI, stroke), we cannot recommend the use of PbO₂ monitoring in determining when to administer a RBC transfusion. *Consensus panel expertise, 91% Agreement, (n=35), Median 8 IQR 8-8.*

Rationale

There are no clinical trials in pediatric or adults with ABI evaluating the use of invasive brain oxygenation monitoring to guide RBC transfusion. One small study suggested a transient effect on brain oxygen tension with RBC transfusion (15). There is no evidence to support the use of this technology to help guide RBC transfusion in this population.

RECOMMENDATIONS FOR RESEARCH

Recommendations

R5.1—In critically ill children with acute brain injury (e.g., trauma, stroke), we recommend further clinical trials testing the transfusion threshold or Hb 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 or not to transfuse RBCs. *Consensus panel expertise, 94% Agreement, (n=35), Median 9, IQR 8-9*

Rationale

As discussed above, there is limited evidence to guide RBC transfusion practice in children with ABI. Further clarity is needed from informative physiology studies, but more so from well designed randomized clinical trials to examine how to best determine the optimal transfusion threshold to improve long-term neurological functional outcomes. In particular, the primary outcome measure must be a functional neurological measure considering that mortality or overall organ dysfunction are not optimal in neurocritically ill populations. Also, specific populations need to be studied separately, (e.g. sTBI, stroke) since the physiology of oxygen delivery and extraction by brain tissue differ.

SUMMARY

The clinical evidence to guide RBC transfusion decision-making for children with ABI is almost non-existent; the guidelines committee has had to examine published management

protocols and data from the literature in adults with ABI. While consensus was reached with very strong agreement on the recommendation to consider RBC transfusion for pediatric ABI patients with a Hb of 7.0 to 10.0 g/dL, and to not use PbO₂ monitors to guide transfusion decisions, much work remains to answer important questions about the safety and efficacy of RBC transfusion in this patient population.

Acknowledgments

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 (CDI-EI-2015-499) and the University of Massachusetts Medical School.

We thank all members of the TAXI initiative for their support and their comments. The study was supported by grants from the Washington University Children's Discovery Institute (CDI-EI-2015-499), University of Massachusetts, CHU Sainte-Justine Foundation, National Institute of Child Health Development (1 R13 HD088086-01), National Heart, Lung and Blood Institute, 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.

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*, Evidenced-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*

References

1. Spinella PC, Doctor A. Role of transfused red blood cells for shock and coagulopathy within remote damage control resuscitation. *Shock*. 2014; 41:30–34. [PubMed: 24296434]
2. Bembea M, Valentine S, Bateman S, et al. The Pediatric Critical Care Transfusion and Anemia Expertise Initiative Consensus Conference Methodology. *Pediatr Crit Care Med*. 2018;19. in submission.
3. Simma B, Burger R, Falk M, et al. A prospective, randomized, and controlled study of fluid management in children with severe head injury: lactated Ringer's solution versus hypertonic saline. *Crit Care Med*. 1998; 26:1265–1270. [PubMed: 9671379]
4. Wahlström MR, Olivecrona M, Koskinen LO, et al. Severe traumatic brain injury in pediatric patients: treatment and outcome using an intracranial pressure targeted therapy--the Lund concept. *Intensive Care Med*. 2005; 31:832–839. [PubMed: 15838678]
5. Narotam PK, Burjonrappa SC, Raynor SC, et al. Cerebral oxygenation in major pediatric trauma: its relevance to trauma severity and outcome. *J Pediatr Surg*. 2006; 41:505–513. [PubMed: 16516625]
6. Stiefel MF, Udoetuk JD, Storm PB, et al. Brain tissue oxygen monitoring in pediatric patients with severe traumatic brain injury. *J Neurosurg*. 2006; 105:281–286. [PubMed: 17328278]
7. Figaji AA, Zwane E, Thompson C, et al. Brain tissue oxygen tension monitoring in pediatric severe traumatic brain injury. Part 1: Relationship with outcome. *Childs Nerv Syst*. 2009; 25:1325–1333. [PubMed: 19214532]
8. Figaji AA, Zwane E, Graham Fieggen A, et al. The effect of increased inspired fraction of oxygen on brain tissue oxygen tension in children with severe traumatic brain injury. *Neurocrit Care*. 2010; 12:430–437. [PubMed: 20232264]
9. Thomale UW, Graetz D, Vajkoczy P, et al. Severe traumatic brain injury in children--a single center experience regarding therapy and long-term outcome. *Childs Nerv Syst*. 2010; 26:1563–1573. [PubMed: 20177687]
10. Stippler M, Ortiz V, Adelson PD, et al. Brain tissue oxygen monitoring after severe traumatic brain injury in children: relationship to outcome and association with other clinical parameters. *J Neurosurg Pediatr*. 2012; 10:383–391. [PubMed: 22978637]
11. Welch TP, Wallendorf MJ, Kharasch ED, et al. Fentanyl and Midazolam Are ineffective in reducing episodic intracranial hypertension in severe pediatric traumatic brain injury. *Crit Care Med*. 2016; 44:809–818. [PubMed: 26757162]
12. Desjardins P, Turgeon AF, Tremblay M-H, et al. Hemoglobin levels and transfusion in neurocritically ill patients: a systematic review of comparative studies. *Crit Care*. 2012;16–R54.

13. Boutin A, Chasse M, Shemilt M, et al. Red blood cell transfusion in patients with traumatic brain injury: a systematic review and meta-analysis. *Transfus Med Rev.* 2016; 30:15–24. [PubMed: 26409622]
14. Lacroix J, Hébert PC, Hutchison JS, et al. Transfusion strategies for patients in pediatric intensive care units. *N Engl J Med.* 2007; 356:1609–1619. [PubMed: 17442904]
15. Figaji AA, Zwane E, Kogels M, et al. The effect of blood transfusion on brain oxygenation in children with severe traumatic brain injury. *Pediatr Crit Care Med.* 2010; 11:325–31. [PubMed: 19794323]