Published in final edited form as:

Pediatr Crit Care Med. 2018 September ; 19(9) : S114–S120. doi:10.1097/PCC.0000000000001619.

Recommendations on Red Blood Cell Transfusions in Critically Ill Children with Acute Respiratory Failure from the Pediatric Critical Care Transfusion and Anemia Expertise Initiative

Pierre Demaret, MD, MSc¹, Guillaume Emeriaud, MD, PhD², Nabil E. Hassan, MD³, Martin C.J. Kneyber, MD, PhD, FCCM⁴, Stacey Valentine, MD MPH⁵, Scot Bateman, MD⁵, Marisa Tucci, MD, FRCPC², and for the Pediatric Critical Care Transfusion and Anemia Expertise Initiative (TAXI)*, in collaboration with the Pediatric Critical Care Blood Research Network (BloodNet), and the Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network

¹Division of Pediatric Critical Care Medicine, Department of Pediatrics, CHC, Liège, Belgium

²Division of Pediatric Critical Care Medicine, Department of Pediatrics, Sainte-Justine Hospital and Université de Montréal, Montreal, Canada ³Division of Pediatric Critical Care, Children's

Hospital of Illinois, University of Illinois College of Medicine, Peoria Illinois ⁴Division of Pediatric Critical Care Medicine, Department of Pediatrics, Beatrix Children's Hospital, University Medical Center Groningen, The University of Groningen, Groningen, The Netherlands. ⁵Division of Pediatric Critical Care Medicine, Department of Pediatrics, Univeristy of Massachusetts Medical School, Worcester, MA

Abstract

Objective—To present the recommendations and supporting literature for red blood cell (RBC) transfusions in critically ill children with bleeding 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 respiratory subgroup included six 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.

Results—TAXI experts developed 7 recommendations focused on children with acute respiratory failure. All recommendations reached agreement (>80%). Transfusion of RBCs in children with

Correspondence address: Pierre Demaret, MD, MSc, Clinique de l'Espérance - Service de soins intensifs pédiatriques, Rue Saint-Nicolas 447, 4420 Montegnée (Belgium), Phone: + 32-4-224-91-80, Fax: + 32-4-224-91-95, pierre.demaret@chc.be.

*TAXI Members listed in Appendix 1

Copyright form disclosure: The remaining authors have disclosed that they do not have any potential conflicts of interest.

respiratory failure with an Hb level < 5g/dL was strongly recommended. It was strongly recommended that RBCs not be systematically administered to children with respiratory failure who are hemodynamically stable and who have a Hb level ≥ 7 g/dL. Experts could not make a recommendation for children with hemodynamic instability, with severe hypoxemia and/or with an Hb level between 5–7g/dL. Specific RBC transfusion strategies using physiologic based metrics and biomarkers could not be elaborated.

Conclusions—The TAXI Consensus Conference developed specific recommendations regarding RBC transfusion management in critically ill children with respiratory failure, as well as recommendations to guide future research. Clinical recommendations emphasize relevant hemoglobin thresholds. Research recommendations emphasize the need to identify appropriate physiological thresholds, suggest a better understanding of alternatives to RBC transfusion, and identify the need for better evidence on Hb thresholds that might be used in specific subpopulations of critically ill children.

Keywords

Transfusion; erythrocyte; hemoglobin; anemia; respiratory failure; hypoxemia; red blood cell; intensive care; child; pediatric critical care; evidence-based; consensus conference

Introduction

Anemia is very common in pediatric intensive care units (PICU), with 74% of critically ill children with a PICU stay of more than 2 days experiencing a hemoglobin (Hb) level below normal at PICU admission or during the PICU stay. As a consequence of anemia, up to 49% of these critically ill children receive at least one red blood cell (RBC) transfusion during their PICU stay (1).

Oxygen delivery (DO₂) is a fundamental concept for the management of critically ill patients. The final goal of resuscitation maneuvers is to maintain or restore adequate oxygen delivery and consumption (2). DO₂ is defined as the product of cardiac output (CO) and arterial content of oxygen (CaO₂) (DO₂ = CO × CaO₂) (3). The CaO₂ depends mainly on the Hb concentration and its saturation in O₂: children suffering from anemia and respiratory distress are thus at increased risk of altered oxygen delivery.

It has been shown that PICU physicians frequently use RBC transfusions in order to improve oxygen delivery (4). However, respiratory adverse events can be caused by RBC transfusions, including transfusion-related acute lung injury, transfusion-associated circulatory overload and transfusion-associated respiratory dysfunction (5), all of which may compromise diffusion of oxygen from the alveoli to the blood. Moreover, storage lesions (i.e., modifications of RBCs during storage) can reduce the ability of the transfused RBCs to bring oxygen to the cells. For example, stored RBCs may show a reduced membrane deformability compromising their passage in the microcirculation (6), or NO signaling may be compromised by storage which may lead to transfusion-induced acute microvascular dysregulation (7, 8). Thus, while it is indisputable that RBC transfusion increases blood oxygen content, it is not clear that stored RBCs are as helpful as expected to improve oxygen delivery to the cells. It is therefore of high importance to define appropriate transfusion

strategies for critically ill children, and it is highly relevant to pay particular attention to children with acute respiratory distress who are at high risk for inadequate oxygen delivery.

Methods

The details of the methodology are described elsewhere in this supplement of *Pediatric Critical Care Medicine* (9). 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 respiratory failure 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. Six experts coordinated the acute respiratory failure 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 acute respiratory failure were divided into two categories: clinical recommendations, and research recommendations.

Our recommendations utilize the criteria of severe hypoxemia, as defined in the in the Transfusion Requirement In Pediatric Intensive Care Unit (TRIPICU) study (10). In TRIPICU, hypoxemia was defined as an SpO₂ < 90% on pulse oximeter with an FiO₂ > 60%. We used these criteria to define severe hypoxemia for our recommendations, considering that the TRIPICU study is currently the most solid available evidence to guide RBC transfusions in critically ill children. However, recently, the Pediatric Acute Lung Injury Consensus Conference (PALICC) Group defined severe pediatric acute respiratory distress syndrome (PARDS) based on an oxygenation index (OI) > 16 or, if PaO₂ not available, on an oxygen saturation index (OSI) > 12.3 (11). We acknowledge that these criteria (rather than the TRIPICU criteria) should probably be used to define severe hypoxemia in future studies on RBC transfusion strategies in critically ill children with respiratory failure.

Results

Using the search strategy described above, we retrieved 5428 abstracts. Eighty-three papers were retained for the full-text evaluation, among which 25 papers were selected and used in the final process to generate recommendations, good practice statements and research questions and are presented in the Supplemental Digital Content 1.

The final recommendations and rationale for transfusion in critically ill children with respiratory failure are presented below.

2.1 We recommend RBC transfusion for critically ill children with respiratory failure who have a Hb concentration < 5 g/dL. Strong recommendation, Low quality pediatric

evidence (1C). Voting data (n=35): 100% agreement, median 9, interquartile range (IQR) 8–9.

Rationale

In children, respiratory distress has been shown to be associated with increased mortality in the context of severe anemia. In a descriptive study of 1866 children admitted to a Kenyan hospital with a primary diagnosis of anemia, the mortality reported by Marsh *et al* (12) was 1.3% if severe anemia (Hb < 5g/dL) was present without respiratory distress and increased to 22.7% if severe respiratory distress was present. English *et al* (13) reported that among 1516 children with malaria and severe anemia (Hb < 5g/dL) hospitalized in Kenya, mortality did not differ between transfused and non-transfused children when considering the entire group (5% *versus* 7%, respectively), but was significantly reduced in transfused children with respiratory distress (11% *versus* 25% for non-transfused children with respiratory distress). In 2433 anemic African children with respiratory distress and a Hb less than 4.7g/dL Lackritz *et al* (14) observed that those who were transfused had a reduced risk of mortality as compared to those not transfused (OR 0.19, 95%CI (0.09, 0.41)); there was no association between receiving a transfusion and mortality among children without respiratory distress regardless of the Hb level at admission. In a subsequent study, Lackritz *et al* (15) enrolled 303 children with a Hb level < 5 g/dL; 116 (38%) who did not receive a transfusion, mostly because blood products were not available. Each child with severe anemia was matched with the next child hospitalized with a Hb > 5 g/dL. Mortality was 19.5% in 303 patients with a Hb > 5 g/dL who were not transfused, 21.4% in 187 patients with a Hb < 5 g/dL who were transfused, and 41.4% in 116 patients with a Hb < 5 g/dL who were not transfused. These researchers thus confirmed that in severely anemic children (Hb < 5g/dL), RBC transfusion had the greatest impact on survival when clinical signs of respiratory distress were present; furthermore, they reported that the benefit of transfusion was limited to the first 2 days of hospitalization.

In a study involving 241 children admitted to the hospital with severe malaria and metabolic acidosis, Akech *et al* (16) observed that it was safe to apply the World Health Organization (WHO) guidelines, i.e. to transfuse 20mL/kg of whole blood if the Hb is < 4g/dL or if it is < 5g/dL and associated with respiratory distress. Indeed, the in-hospital mortality was 7.7% for children with severe symptomatic malaria at admission requiring urgent transfusion according to WHO guidelines, and 8.8% for children who did not fulfill the WHO transfusion criteria at the time of admission to hospital but who were transfused later during the course of their admission. Moreover, the restrictive transfusion strategy suggested by the WHO did not affect hematological recovery, which was identical for transfused survivors (n=61, including 46 (76%) with respiratory distress) and non-transfused survivors (n=97, including 54 (56%) with respiratory distress): the Hb at hospital discharge was 6.4±1.5g/dL *versus* 6.8±1.6g/dL respectively (p=0.08), and the follow-up Hb (within 22 to 35 days post-admission) was 10.2±1.7g/dL *versus* 10.0±1.3g/dL, respectively (p=0.25).

It must be noted that all these observations were made in patient populations in whom severe anemia arose from various acute, subacute and chronic illnesses, which might have confounded the beneficial impact of receiving a transfusion. Moreover, these studies on

children with severe anemia were conducted in Africa, which may limit the generalizability of the results to other populations in other countries.

Adult data also show that severe anemia is associated with worse outcomes, especially when the Hb level falls below 5 g/dL (17–19). In a retrospective cohort study performed in 1958 adult patients who underwent surgery and declined blood transfusion for religious reasons, Carson *et al* (20) found a mortality of 1.3% in patients with preoperative Hb ≥ 12 g/dL versus 33.3% in patients with preoperative Hb < 6 g/dL. It is interesting to note that, among those with a postoperative Hb < 6 g/dL who died in the hospital, 35.9% had a respiratory failure at the time of death (21). *GRADE 1C based on upgrading for large treatment effect, and downgrading for imprecision and indirectness-observational studies.*

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 Hb concentration is ≥ 7 g/dL. Strong recommendation, Moderate quality pediatric evidence (1B). Voting data (n=29): 100% agreement, median 8.5, IQR 8–9.

Rationale

The TRIPICU study showed that a restrictive RBC transfusion strategy (i.e., to transfuse when the Hb level is < 7 g/dL) is not inferior to a liberal strategy (i.e., to transfuse when the Hb level is < 9.5 g/dL) in children who are hemodynamically stable (i.e., children whose mean arterial pressure is not less than 2 standard deviations below normal mean for age and whose cardiovascular support has not been increased in the last 2 hours), but leads to a significant decrease of exposure to RBC transfusions (10). Indeed, the 320 children randomized in the restrictive-strategy group and the 317 children randomized in the liberal-strategy group showed the same outcomes (incidence of new or progressive multiple organ dysfunction syndrome (NPMODS): 12% in each group, absolute risk reduction 0.4% (95%CI (0.61, 1.49), $p=0.84$), but the proportion of non-transfused children was 54% in the restrictive-strategy group versus 2% in the liberal-strategy group ($p<0.001$).

Among the 637 children included in the TRIPICU study, 480 (75.4%) had respiratory dysfunction at the time of admission to PICU. Respiratory dysfunction was defined as the presence of any one of the following criteria: 1) Respiratory rate > 90 breaths/min (< 1 yr) or > 70 breaths/min (≥ 1 yr); 2) PaO₂ < 40 torr (5.3 kPa) in absence of cyanotic heart disease; 3) PaCO₂ > 65 torr (8.7 kPa); 4) PaO₂/FiO₂ < 200 in absence of cyanotic heart disease; 5) mechanical ventilation (> 24 hr if postoperative). The incidence of NPMODS in these children was 14.1% in the restrictive group versus 14.2% in the liberal group. *GRADE 1B based on downgrading for imprecision (single high quality RCT).*

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. Voting data (n=29): 97% agreement, median 8, IQR 8–9.

Rationale

This recommendation is in accordance with the recent PALICC (11), in which children with severe hypoxemia were excluded from the recommendation on the safety of a restrictive transfusion strategy (Hb threshold 7g/dL) in children with PARDS.

Some children included in the TRIPICU study had ARDS (n=48, including 23 children in the restrictive group and 25 children in the liberal group) or acute lung injury (ALI) (n=73, including 38 children in the restrictive group and 35 children in the liberal group) on admission to PICU (defined according to the criteria prior to the Berlin criteria, i.e., the 1994 American-European Consensus Conference (AECC) definition of ARDS (22)). Among them, 18/61 (29.5%) in the restrictive group versus 15/60 (25%) in the liberal group developed NPMODS subsequently, with no statistical difference but with a statistical power inferior to 10%. Thus, data from the TRIPICU study indicate that a restrictive transfusion strategy could be safe in children with hypoxemic respiratory failure.

However, it is important to highlight that 65 children screened for TRIPICU were excluded from the study because of hypoxemia, defined by $SpO_2 < 90\%$ despite FiO_2 of at least 60%. Moreover, 7 children were temporarily suspended from the research protocol because of the occurrence of an “ARDS with overt systemic hypoxemia”. The results of the TRIPICU study must thus be interpreted cautiously for children with respiratory failure and severe hypoxemia: no firm conclusion can be drawn from TRIPICU to guide RBC transfusions in these children.

Despite the lack of solid evidence to guide RBC transfusions in children with respiratory failure and hypoxemia, it must be emphasized that RBC transfusions have been shown to be associated with worsening of respiratory function, especially in critically ill children. For example, the incidence of transfusion related acute lung injury may be higher in children admitted to PICU than in the general pediatric population (23). Moreover, several observational studies have described an association between RBC transfusions and respiratory complications, even after adjustment for potential confounders in multivariable models: RBC transfusions have been found to be associated with worsening of oxygenation (24–26), with increased duration of mechanical ventilation (5,24–33), with an increased risk of respiratory dysfunction (1, 26) and with an increased risk of ventilatory-associated pneumonia (34). Obviously, these observational data do not permit establishment of a cause-effect relationship, but these reproducible findings must be kept in mind at the time of prescribing an RBC transfusion for a child with respiratory distress.

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

Rationale

The Transfusion Requirements In Critical Care (TRICC) study showed that a restrictive transfusion strategy was safe in most critically ill adults. In this study, published 8 years

before the TRIPICU study, the restrictive and the liberal thresholds (Hb levels of 7 and 9g/dL, respectively) were chosen based on stated transfusion practices in adult ICUs. Indeed, a survey conducted among 193 Canadian critical care physicians had shown that the baseline Hb transfusion threshold averaged from 8.3 ± 1 g/dL to 9.5 ± 1 g/dL depending on the clinical scenario proposed (35). The thresholds used in the TRICC study were subsequently retained based on these stated practices so that critical care physicians would not be reluctant to participate in the study. The same methodology was used to select the Hb thresholds for the TRIPICU study. Laverdière *et al* (36) assessed transfusion practices in Canadian and European PICUs using an international survey. In that survey, most of the participating PICU physicians responded that they would use a Hb threshold of 7 to 10g/dL to prescribe RBCs in critically ill children.

Thus, the restrictive thresholds used in both the adult and the pediatric RCT, which led to the current recommendations on RBC transfusions in critically ill patients, are based on stated practices at the time of the design of these studies. As described above, observational data indicate that severe anemia is associated with worse outcomes and it is recommended that RBCs be administered when the Hb level is below 5g/dL. However, there are no data indicating that a Hb threshold of 7g/dL is safer than a threshold between 5 and 7g/dL. Until more data are available, it is reasonable to use clinical judgment for children with a Hb level in this “5–7g/dL grey zone”.

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. Voting data (n=35): 100% agreement, median 8, IQR 8–9.

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. Voting data (n=35): 97% agreement, median 9, IQR 8–9.

Rationale

Assessment of the accuracy of oxygen delivery is important to guide decision-making with regard to RBC transfusion in the critically ill. Traditional ways to measure this have included measurement of lactate, central (or mixed) venous oxygen saturation (ScvO₂), and global hemodynamic markers such as mean arterial pressure and cardiac index. More recently, focus has been placed on other methods to detect derangements in oxygen delivery and/or utilization that are non invasive, reliable, and sensitive such as near-infrared spectroscopy (NIRS) to assess regional tissue oxygenation, as well as bedside ultrasound techniques to assess the macrovascular hemodynamic factors in oxygen delivery (37). All these biomarkers and metrics, many of which are surrogate markers of oxygen metabolism, reveal information about oxygen delivery and consumption but cannot be utilized as therapeutic targets at the present time unless they are more robustly assessed and shown to have clinical applicability and to be of value in clinical decision-making with regard to RBC transfusion. To date no study has demonstrated a clinical benefit of using transfusion

strategies guided by physiologic markers in children (including children with respiratory failure).

R2.2 We recommend that further studies are needed 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. Voting data (n=35): 100% agreement, median 9, IQR 8–9.

Rationale

Children with severe hypoxemia and/or hemodynamic instability obviously are at increased risk of inadequate oxygen delivery, and it has been shown that PICU physicians frequently use RBC transfusions in an effort to improve oxygen delivery (4). However, several issues may impair the ability of stored RBCs to improve oxygen delivery to the cells. For example, the storage lesions affect membrane deformability and can cause compromised NO signaling leading to acute microvascular dysregulation (6, 38). Moreover, RBC transfusions may contribute to respiratory failure: new or progressive respiratory dysfunction may be observed after RBC transfusion (5), and a circulatory overload associated with transfusion may occur and worsen gas exchange (39). It is thus of great importance to develop appropriate transfusion strategies for critically ill children with respiratory failure, particularly for those with severe hypoxemia or hemodynamic instability.

Conclusions

The evidence to guide RBC transfusions in critically ill children with respiratory failure is scarce to date, especially for children with hypoxemia and/or hemodynamic instability. Observational data indicate that respiratory distress worsens the prognosis of children with severe anemia. On the other hand, there are data showing that RBC transfusions may worsen respiratory failure. Determining appropriate transfusion strategies is thus of utmost importance for these children.

Based on the currently available evidence, we strongly recommend 1/ transfusion of RBCs in children with respiratory failure who have a Hb < 5g/dL, and 2/ not to administer RBCs to non-severely hypoxemic, non-cyanotic, and hemodynamically stable children with respiratory failure who have a Hb $\geq$ 7 g/dL. Studies are urgently required to develop appropriate decision-making processes to guide RBC transfusions in children with respiratory failure, especially in children with severe hypoxemia and/or hemodynamic instability. These processes should include an adequate Hb threshold as well as physiologic markers aiming to assess the appropriateness of the balance between oxygen consumption and oxygen delivery.

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.

Dr. Valentine's institution received funding from Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) and National Heart, Lung, and Blood Institute (NHLBI) under award number 1 R13 HD088086-01; the Society for the Advancement of Blood Management (SABM) SABM-Haemonetics Research Starter Grant; and the 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 National Institutes of Health (NIH); the SABM SABM-Haemonetics Research Starter Grant; CHU-Sainte-Justine Foundation; Washington University Children's Discovery Institute; and the University of Massachusetts Medical School. Dr. Emeriaud's institution received funding from a research award by the Fonds de recherche du Québec-Santé. Dr. Bateman's institution received funding from the NICHD and NHLBI (R13 grant), and he received support for article research from the NIH.

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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*