Published in final edited form as:

Pediatr Crit Care Med. 2018 September ; 19(9) : S127–S132. doi:10.1097/PCC.0000000000001605.

Recommendations on Red Blood Cell Transfusion in Critically Ill Children with Non-Life Threatening Bleeding or Hemorrhagic Shock from the Pediatric Critical Care Transfusion and Anemia Expertise Initiative

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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 bleeding subgroup included five experts. Electronic searches were

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

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 Consensus Conference experts developed a total of 6 recommendations focused on transfusion in the critically ill child with acute bleeding. In critically ill children with non-life threatening bleeding, we recommend giving a RBC transfusion for a Hb concentration < 5 g/dL, and be considered for a Hb concentration between 5–7 g/dL. In critically ill children with hemorrhagic shock, we suggest that RBCs, plasma and platelets transfusion ratio between 2:1:1 to 1:1:1 until the bleeding is no longer life-threatening. We recommend future studies to develop physiologic and laboratory measures to indicate the need for RBC transfusions, and to determine if goal directed hemostatic resuscitation improves survival. Finally, we recommend future studies to determine if low titer group O whole blood is more efficacious and safe compared to reconstituted whole blood in children with hemorrhagic shock.

Conclusions—The TAXI Consensus Conference developed pediatric specific recommendations regarding RBC transfusion management in the critically ill child with acute bleeding, as well as recommendations to help guide future research priorities.

Keywords

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

Introduction

Bleeding is very common in a pediatric critical care setting. In an observational study of 450 patients admitted to a pediatric intensive care unit (PICU), forty-five (10%) had clinically significant bleeding at admission, and 37 (8%) developed clinically significant bleeding during their PICU course (1). Bleeding was associated with longer time on vasopressor therapy and longer PICU length of stay. Bleeding leads to two physiological insults that contribute to reduced oxygen delivery: decreased red blood cell (RBC) mass which decreases blood oxygen content and hypovolemia which decreases cardiac output.

The objective of the hemorrhage subgroup of the Pediatric Critical Care Transfusion and Anemia Expertise Initiative (TAXI) was to critically review the current literature on RBC transfusions in critically ill children with non-life threatening bleeding or hemorrhagic shock to determine recommendations for clinical practice and future research.

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 hemorrhagic shock in critically ill children. We searched references from identified articles for additional publications. Two authors reviewed all citations independently. We used a standardized data extraction form to construct evidence tables and graded the evidence using

the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. A panel of 38 experts from 29 academic institutions in 8 countries met over the course of two years to develop evidence-based and, when evidence was lacking, expert-based recommendations for RBC transfusion in critically ill children. Five experts coordinated the bleeding subgroup. Hemorrhagic shock was defined as severe bleeding in patients at risk of exsanguination. 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 bleeding were divided into two categories: clinical recommendations, and research recommendations.

Results

Two members independently reviewed 4399 abstracts and identified 95 articles for full-text evaluation. Only two randomized controlled trials (RCTs) and two observational studies were included to support pediatric clinical recommendations. Two additional RCTs in adults were retained for supporting the rationale. The final recommendations and rationale for transfusion in critically ill children with non-life threatening bleeding and hemorrhagic shock are presented below. Although transfusion in these children are not limited to the following indication, our recommendations focused on hemorrhage. The references that were used to reach these recommendations are presented in Supplemental Digital Data, Supplemental Table 1.

Non-life threatening bleeding

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

Rationale—In critically ill children, the current evidence suggests that a Hb concentration < 5 g/dL is associated with an increased risk of mortality. In a large observational study in Kenya, Lacritz et al showed that children admitted with a Hb concentration < 5 g/dL had a higher risk of mortality than those with higher Hb concentrations (18% versus 8%, $p=0.001$).⁽³⁾ Whole blood transfusions, which were available to only 20% of those patients, decreased mortality in children with clinical signs of respiratory distress and Hb < 4.7 g/dl (OR 0.19; 95%CI 0.09–0.41). These patients were different from those admitted in most PICUs and the treatment was not RBC units but whole blood. However, there is no evidence to suggest that a lower threshold is safe. *GRADE 2C is based on downgrading for risk of bias, indirectness, and imprecision.*

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

Rationale—In critically ill children with non-life threatening bleeding, the current evidence suggests that transfusion is not required if the Hb concentration is above 7 g/dL. In

a large randomized controlled trial, Lacroix et al showed that waiting until the Hb concentration drops to 7 g/dL is not inferior to transfusing for an Hb concentration threshold of 9 g/dL (4). Subgroup analyses confirmed that this restrictive RBC transfusion strategy is safe in critically ill children admitted in a PICU after general surgery (5) and cardiac surgery (6). However, these studies did not provide explicit information on the bleeding status of the patients.

One randomized controlled trial evaluated RBC transfusion strategies in pediatric cardiac surgery patients, aged 6 weeks to 6 years (7). Prior to surgery, 107 patients were randomly assigned to one of two groups with specific RBC transfusion thresholds: Hb 10.8 g/dl (liberal transfusion strategy) and Hb 8.0 g/dl (restrictive transfusion strategy). When a threshold was reached, each patient was to receive an RBC transfusion of 10 ml/kg. The transfusion policy adherence was expected from induction of anesthesia until hospital discharge. The average blood loss in chest tubes was 16 ml/kg. Patients in the restrictive arm were less transfused than those in the liberal group. There were no differences in clinical outcome in terms of complications, hours of mechanical ventilation, or PICU length of stay, apart from a statistically significant one day decrease in the hospital length of stay ($p=0.047$). As this study did not report the proportion of patients who were actively bleeding, it was not included in the references leading to this recommendation.

There are some adult data suggesting that in some bleeding situations, a restrictive transfusion strategy is superior to a liberal study. Villanueva et al showed that a RBC transfusion threshold of 7 g/dL improved outcomes in patients with acute upper gastrointestinal bleeding, when compared to a threshold of 9 g/dL (8). However, these results should not be generalized to other bleeding populations, especially children.

There is a knowledge gap for the Hb concentration between 7 g/dL and 5 g/dL in bleeding critically ill children. Indeed, no pediatric trial has investigated the safety of transfusion threshold below 7 g/dL. In adults, Carson et al described the clinical outcome of 2083 patients who underwent surgery but declined transfusions for religious reasons (9). After adjusting for age, cardiovascular disease, and severity of disease, the odds of death in patients with a postoperative Hb concentration < 8 g/dL increased 2.5 times (95% CI, 1.9–3.2) for each g/dL decrease in Hb concentration. However, as children have different DO_2/VO_2 physiological reserves, different baseline Hb levels (which vary with age), and co-morbidities (fewer coronary disease, more congenital malformation), adult results might not be extrapolated to critically ill children who are bleeding.

Hemorrhagic shock

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. Voting Data (n=35): 94% Agreement, Median 9, IQR 8-9.*

Rationale—There is little high-quality evidence defining the optimal approach to fluid resuscitation and transfusion in children with hemorrhagic shock. The management of acute life-threatening bleeding has been most extensively studied in adult trauma, where

hemostatic resuscitation has become the predominant approach to managing massive transfusion.

The paradigm of hemostatic resuscitation centers on the administration of fresh frozen plasma, platelets, and RBCs in ratios that approximate physiologic composition. The biological rationale for this approach is that empiric replacement of soluble clotting factors and cellular elements lost during active hemorrhage prevents or attenuates the dilutional coagulopathy that would otherwise predictably occur with traditional component therapy. Additionally, following trauma, preemptive administration of platelets and clotting factors treats trauma-induced coagulopathy that develops independently of iatrogenic dilutional mechanisms.

A number of observational studies have been published in which hemostatic resuscitation has been associated with improved bleeding, hospital, and mortality outcomes(10–15), leading many trauma centers and the US military to adopt this practice (16). These observational studies have inherent weaknesses, most notably selection and survival bias. In 2015 the Pragmatic, Randomized Optimal Platelet and Plasma Ratios (PROPPR) results were published where RBC, fresh frozen plasma, and platelet transfusion ratios of 2:1:1 and 1:1:1 were compared in adult trauma patients (17). No differences were in 24-hour and 30-day mortality between the two groups. However, the 1:1:1 ratio was associated with a greater percentage of patients achieving hemostasis and a reduction in deaths due to exsanguination in the first 24 hours following injury, without a difference in complications between the two groups.

Although children are generally not represented in these studies, it may be reasonable to believe that the same hemostatic resuscitation principles and biology (hemodilution of coagulation factors) apply to children. No studies have demonstrated survival benefits of hemostatic resuscitation strategies in children, although the implementation of a 1:1:1 massive transfusion protocol in a pediatric setting was reported without an increase in total blood products transfused or an increase in in-hospital morbidity (18).

Research recommendations

R4.1 In children with non-life threatening bleeding, we recommend future studies to develop physiologic and laboratory measures to indicate the need for RBC transfusions. *Consensus panel expertise. Voting Data (n=35): 94% Agreement, Median 8, IQR 8-9.*

Rationale—Assessing the balance between oxygen delivery (DO_2) and oxygen consumption (VO_2) is critical to guide decision-making with regard to RBC transfusion, especially in the critically ill children who are bleeding. This DO_2/VO_2 balance is frequently evaluated by measuring lactate levels and central (or mixed) venous oxygen saturation (ScvO_2). New methods, such as near-infrared spectroscopy (NIRS) are increasingly used. In a recent trial, Leal-Noval et al randomized 101 neurocritically ill adult with hemoglobin level between 7 and 10 g/dL to receive RBC transfusions to attain an transcranial oxygen saturation > 60% (NIRS arm) or to maintain hemoglobin between 8.5 and 10 g/dL (hemoglobin arm) (19). Among patients with hemoglobin levels of 7.0 to 8.5 g/dL, withholding transfusion until transcranial oxygen saturation is <60% may result in

reduced RBCs requirements compared with routinely transfusing to attain a hemoglobin level >8.5 g/dL. Unfortunately, despite their frequent use, these surrogate markers of oxygen metabolism have not been assessed in critically ill children who are bleeding. Furthermore, the association between these markers and neurodevelopment are unknown.

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

Rationale—Early identification and correction of coagulopathy in concert with reversal of any shock state is a vital component of the resuscitation of critically ill children with hemorrhagic shock. Currently, results from viscoelastic monitoring (VEM) assays such as thromboelastography and rotational thromboelastometry as well as conventional coagulation tests (CCT), such as prothrombin time, international normalized ratio, partial thromboplastin time, and platelet count, can be employed to monitor and direct hemostatic resuscitation in patients with life-threatening hemorrhage. A single center, pragmatic randomized, prospective study of civilian adult trauma patients receiving massive transfusion protocol activation showed that a goal directed hemostatic resuscitation strategy using VEM compared to CCT had improved survival (20). Multiple studies in adult trauma patients have shown survival benefits to resuscitation with an empiric ratio of red blood cells, plasma, and platelets – particularly in the context of massive transfusion protocols and damage control resuscitation (14, 17, 21–23). The impact of empiric ratio resuscitation in children with hemorrhagic shock remains unclear with conflicting results from multiple retrospective registry and single center studies (18, 24–30). No prospective studies are available. Similarly, there is a significant evidence gap regarding the use of goal directed hemostatic resuscitation strategies, using VEM or CCT, in children with life-threatening hemorrhage. Of note, a recent survey of Pediatric Trauma Society members showed a desire to implement VEM to guide trauma resuscitations (31). Finally, there are also no prospective studies comparing empiric ratio-based transfusion resuscitation strategies with VEM or CCT guided transfusion in children. Given the paucity of the existing pediatric evidence, the significance of coagulopathy and hemorrhagic shock in children, and the importance of early identification and rapid correction of coagulopathy, well-designed, prospective studies are sorely needed to identify the most appropriate resuscitation strategy in this patient population.

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

Rationale—Hemostatic resuscitation is based on the concept that a blood-based transfusion strategy that is balanced in improving oxygen delivery and hemostasis is optimal for life-threatening hemorrhage. Historically, whole blood transfusions had been the primary resuscitative strategy for hemorrhagic shock; however, this had fallen out of favor due to the advent of component therapy in the 1970's (32). Currently, there is a resurgent interest in use

of low titer group O whole blood transfusion for life-threatening bleeding (33). Figure 1 lists the potential benefits of low titer group O whole blood compared to components. With the resurgence of utilization of whole blood for resuscitation in both civilian and military settings, studies in children with hemorrhagic shock are needed to determine if low titer group O whole blood is efficacious and safe when compared to component therapy.

Conclusions

The TAXI Consensus Conference developed pediatric specific recommendations regarding RBC transfusion management in the critically ill child with non-life threatening bleeding and hemorrhagic shock. In critically ill children with non-life threatening bleeding, we recommend that a RBC transfusion should be given for a Hb concentration < 5 g/dL, and to be considered for a Hb concentration between 5–7 g/dL. In critically ill children with hemorrhagic shock, we suggest that RBCs, plasma and platelets transfusion ratio between 2:1:1 to 1:1:1 until the bleeding is no longer life-threatening. From a research standpoint, we recommend future studies to develop physiologic and laboratory measures to indicate the need for RBC transfusions, and to determine if goal directed hemostatic resuscitation improves survival. Finally, we recommend future studies to determine if low titer group O whole blood is more efficacious and safe compared to reconstituted whole blood in children with hemorrhagic shock.

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), SABM SABM-Haemonetics Research Starter Grant, CHU-Sainte-Justine Foundation, Washington University Children's Discovery Institute, and the University of Massachusetts Medical School. Dr. Bateman's institution received funding from an R13 conference grant from the NICHD and NHLBI and from SABM, and he received support for article research from the NIH. Dr. Spinella received funding from New Health Sciences.

References

1. White LJ, Fredericks R, Mannarino CN, et al. Epidemiology of Bleeding in Critically Ill Children. *J Pediatr*. 2017; 184:114–119. [PubMed: 28185627]
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 (xx Suppl): in submission.

3. Lackritz EM, Campbell CC, Ruebush TK 2nd, et al. Effect of blood transfusion on survival among children in a Kenyan hospital. *Lancet*. 1992; 340:524–528. [PubMed: 1354285]
4. Lacroix J, Hébert PC, Hutchison JS, et al. Transfusion strategies for patients in pediatric intensive care units. *NEJM*. 2007; 356:1609–1619. [PubMed: 17442904]
5. Rouette J, Trottier H, Ducruet T, et al. Red blood cell transfusion threshold in postsurgical pediatric intensive care patients: a randomized clinical trial. *Annals of surgery*. 2010; 251:421–427. [PubMed: 20118780]
6. Willems A, Harrington K, Lacroix J, et al. Comparison of two red-cell transfusion strategies after pediatric cardiac surgery: a subgroup analysis. *Crit Care Med*. 2010; 38:649–656. [PubMed: 19789443]
7. de Gast-Bakker DH, de Wilde RB, Hazekamp MG, et al. Safety and effects of two red blood cell transfusion strategies in pediatric cardiac surgery patients: a randomized controlled trial. *Intensive Care Med*. 2013; 39:2011–2019. [PubMed: 23995984]
8. Villanueva C, Colomo A, Bosch A, et al. Transfusion Strategies for Acute Upper Gastrointestinal Bleeding. *NEJM*. 2013; 368:11–21. [PubMed: 23281973]
9. Carson JL, Noveck H, Berlin JA, et al. Mortality and morbidity in patients with very low postoperative Hb levels who decline blood transfusion. *Transfusion*. 2002; 42:812–818. [PubMed: 12375651]
10. Borgman MA, Spinella PC, Perkins JG, et al. The ratio of blood products transfused affects mortality in patients receiving massive transfusions at a combat support hospital. *J Trauma*. 2007; 63:805–813. [PubMed: 18090009]
11. Shaz BH, Dente CJ, Nicholas J, et al. Increased number of coagulation products in relationship to red blood cell products transfused improves mortality in trauma patients. *Transfusion*. 2010; 50:493–500. [PubMed: 19804568]
12. Cotton BA, Reddy N, Hatch QM, et al. Damage control resuscitation is associated with a reduction in resuscitation volumes and improvement in survival in 390 damage control laparotomy patients. *Ann Surg*. 2011; 254:598–605. [PubMed: 21918426]
13. Holcomb JB, del Junco DJ, Fox EE, et al. The prospective, observational, multicenter, major trauma transfusion (PROMMTT) study: comparative effectiveness of a time-varying treatment with competing risks. *JAMA Surg*. 2013; 148:127–136. [PubMed: 23560283]
14. Johansson PI, Sorensen AM, Larsen CF, et al. Low hemorrhage-related mortality in trauma patients in a Level I trauma center employing transfusion packages and early thromboelastography-directed hemostatic resuscitation with plasma and platelets. *Transfusion*. 2013; 53:3088–3099. [PubMed: 23614333]
15. Langan NR, Eckert M, Martin MJ. Changing patterns of in-hospital deaths following implementation of damage control resuscitation practices in US forward military treatment facilities. *JAMA Surg*. 2014; 149:904–912. [PubMed: 25029432]
16. Callum JL, Rizoli S. Plasma transfusion for patients with severe hemorrhage: what is the evidence? *Transfusion*. 2012; 52(Suppl 1):30S–37S. [PubMed: 22578369]
17. Holcomb JB, Tilley BC, Baraniuk S, et al. Transfusion of plasma, platelets, and red blood cells in a 1:1:1 vs a 1:1:2 ratio and mortality in patients with severe trauma: the PROPPR randomized clinical trial. *JAMA*. 2015; 313:471–482. [PubMed: 25647203]
18. Hwu RS, Spinella PC, Keller MS, et al. The effect of massive transfusion protocol implementation on pediatric trauma care. *Transfusion*. 2016; 56:2712–2719. [PubMed: 27572499]
19. Leal-Noval SR, Arellano-Orden V, Munoz-Gomez M, et al. Red Blood Cell Transfusion Guided by Near Infrared Spectroscopy in Neurocritically Ill Patients with Moderate or Severe Anemia: A Randomized, Controlled Trial. *J Neurotrauma*. 2017; 34:2553–2559. [PubMed: 28486023]
20. Gonzalez E, Moore EE, Moore HB, et al. Goal-directed Hemostatic Resuscitation of Trauma-induced Coagulopathy: A Pragmatic Randomized Clinical Trial Comparing a Viscoelastic Assay to Conventional Coagulation Assays. *Annals of surgery*. 2016; 263:1051–1059. [PubMed: 26720428]
21. del Junco DJ, Holcomb JB, Fox EE, et al. Resuscitate early with plasma and platelets or balance blood products gradually: findings from the PROMMTT study. *J Trauma and Acute Care Surgery*. 2013; 75:S24–30.

22. Holcomb JB, Wade CE, Michalek JE, et al. Increased plasma and platelet to red blood cell ratios improves outcome in 466 massively transfused civilian trauma patients. *Annals of surgery*. 2008; 248:447–458. [PubMed: 18791365]
23. Holcomb JB, Zarzabal LA, Michalek JE, et al. Increased platelet:RBC ratios are associated with improved survival after massive transfusion. *J Trauma*. 2011; 71:S318–328. [PubMed: 21814099]
24. Cannon JW, Johnson MA, Caskey RC, et al. High ratio plasma resuscitation does not improve survival in pediatric trauma patients. *J Trauma and Acute Care Surgery*. 2017; 83:211–217.
25. Galganski LA, Greenhalgh DG, Sen S, et al. Randomized Comparison of Packed Red Blood Cell-to-Fresh Frozen Plasma Transfusion Ratio of 4:1 vs 1:1 During Acute Massive Burn Excision. *J Burn Care Res*. 2017; 38:194–201. [PubMed: 27893574]
26. Edwards MJ, Lustik MB, Clark ME, et al. The effects of balanced blood component resuscitation and crystalloid administration in pediatric trauma patients requiring transfusion in Afghanistan and Iraq 2002 to 2012. *J Trauma and Acute Care Surgery*. 2015; 78:330–335.
27. Nosanov L, Inaba K, Okoye O, et al. The impact of blood product ratios in massively transfused pediatric trauma patients. *American journal of surgery*. 2013; 206:655–660. [PubMed: 24011571]
28. Diab YA, Wong EC, Luban NL. Massive transfusion in children and neonates. *British journal of haematology*. 2013; 161:15–26. [PubMed: 23432321]
29. Chidester SJ, Williams N, Wang W, et al. A pediatric massive transfusion protocol. *J Trauma and Acute Care Surgery*. 2012; 73:1273–1277.
30. Hendrickson JE, Shaz BH, Pereira G, et al. Implementation of a pediatric trauma massive transfusion protocol: one institution's experience. *Transfusion*. 2012; 52:1228–1236. [PubMed: 22128884]
31. Russell RT, Maizlin II, Vogel AM. Viscoelastic monitoring in pediatric trauma: a survey of pediatric trauma society members. *J Surg Res*. 2017; 214:216–220. [PubMed: 28624047]
32. Spinella PC, Cap AP. Whole blood: back to the future. *Curr Opin Hematol*. 2016; 23:536–542. [PubMed: 27607444]
33. Spinella PC, Cap AP. Prehospital hemostatic resuscitation to achieve zero preventable deaths after traumatic injury. *Curr Opin Hematol*. 2017; 24:529–535. [PubMed: 28832355]

Appendix 1

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

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Efficacy

- Improved hemostasis compared to component therapy due to platelets stored at 4C
- More concentrated product due to less anticoagulants and additive solution

Safety

- Reduced risk of incompatible plasma compared to use of non-matched platelets and Type A or AB plasma
- Reduced risk of bacterial contamination compared to platelets at 22C
- Safety record with over 1 million units transfused in combat and civilian settings

Logistic

- Increased access to platelet containing product due to storage duration of at least 21 days for both pre-hospital and in-hospital resuscitation
- More timely access to a balanced administration of all blood components needed to treat hemorrhagic shock

Figure 1.
Benefits of Low Titer Group O Whole Blood Compared to Blood Components for Hemorrhagic Shock (31, 32)