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Damage Control Resuscitation in Pediatric Trauma: What You Need to Know

Robert T. Russell, MD, MPH[1], Christine M. Leeper, MD[2], Philip C. Spinella, MD[2]

[1]Department of Surgery, Division of Pediatric Surgery, University of Alabama at Birmingham, Children's of Alabama, Birmingham, AL.

[2]Department of Surgery and Critical Care Medicine, University of Pittsburgh Medical Center. Pittsburgh, PA.

Corresponding Author:

Robert T. Russell, MD, MPH

University of Alabama at Birmingham

Children's of Alabama

1600 7th Avenue South, Suite 300

Birmingham, AL 35233

205-638-9699

ORCID: 0000-0002-8531-4249

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Robert T. Russell, MD, MPH robert.russell@childrensal.org

Christine M. Leeper, MD leepercm@upmc.edu

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Philip C. Spinella, MD spinella@pitt.edu

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Abstract

Damage control resuscitation consists of rapid control of bleeding, avoidance of hemodilution, acidosis, and hypothermia; early empiric balanced transfusions with red blood cells, plasma and platelets, or whole blood when available, and the use of intravenous or mechanical hemostatic adjuncts when indicated. The principles utilized in pediatric and adult trauma patients are quite similar. There are very important recognized physiologic differences in children with traumatic hemorrhagic shock that warrant slight variations in damage control resuscitation. In pediatric trauma patients, early physiologic signs of shock may be different from adults and the early recognition of this is critical to enable prompt resuscitation and utilization of damage control principles. This review details the current principles of pediatric damage control resuscitation based on the best available literature, expert consensus recommendations, and also describes a practical guide for implementation of damage control resuscitation strategies for pediatric trauma patients.

Keywords: pediatric trauma, resuscitation, transfusion, whole blood, hemorrhagic shock

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Introduction

The principles of damage control resuscitation (DCR) are largely the same in pediatric and adult trauma patients: rapid control of bleeding, avoidance of hemodilution, acidosis, hypocalcemia, and hypothermia; early empiric balanced transfusions with red blood cells, plasma, or platelets, or whole blood when available, and the use of intravenous or mechanical hemostatic adjuncts when indicated.[1] An estimated 1,000 to 2,000 preventable traumatic deaths in children per year occur after injury in the United States because of inadequate or delayed care.[2] Some of these deaths may represent pediatric patients with unrecognized hemorrhagic shock that are not promptly treated with hemorrhage control and appropriate hemostatic resuscitation. The 30-day mortality in children with traumatic hemorrhagic shock is estimated to be 36-50% compared with the 25% reported mortality in similar adults.[3, 4] The early stages of hemorrhagic shock after injury in children can be more challenging to recognize because of their remarkable compensatory mechanisms. In children unlike adults, blood pressure alone is an insensitive indicator of hemorrhagic shock as hypotension is a late sign often not occurring until blood volume is reduced by >40%.[5] Based on the current literature, the challenges health care providers must focus on are the early recognition of shock in the pediatric patient, moving the hemostatic resuscitation forward to the prehospital phase when feasible, improvement in times to first blood product, balanced resuscitation and efficiency of massive transfusion protocols (MTPs).

In a recent multi-institutional prospective observational trial in life-threatening bleeding in children, a significant delay in initiating hemostatic resuscitation was common. The median time from recognition of life-threatening hemorrhage (LTH) to first red blood cells (RBCs)

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administration was 8 minutes (range: 0-42), median time to plasma administration was 34 minutes (range: 15-77), and median time to platelet administration was 42 minutes (range: 15-102). When evaluating the trauma patients specifically, the median duration of MTPs was 3 hours (range: 1.3-5.7).[4] A delay in both the recognition of life-threatening hemorrhage (LTH) and the initiation of hemostatic resuscitation may be one cause of the increased duration of MTP activation and mortality in this population compared to adults.

Prehospital Management of Pediatric Hemorrhagic Shock

Prehospital management of the pediatric patient requiring damage control resuscitation remains challenging for a number of reasons: 1) Uncommon frequency of the event—of all injured children, the percentage requiring blood transfusion and massive transfusion approximately is 2.5% and 0.5%, respectively.[6] This corresponds to an average of 10-20 MTP activation from traumatic injury per year at large pediatric trauma centers, and far fewer at most lower volume centers; 2) relative emergency medical services provider inexperience with this uncommon pediatric event leading to the delay in recognition and treatment of LTH; 3) intravenous access in children can be challenging; combined with the relative unfamiliarity of EMS providers with using intraosseous needle access in children, this can lead to delays in resuscitation[7] while access is being established; and 4) a paucity of quality research to establish evidence-based prehospital pediatric trauma management.

The recently published Pediatric Traumatic Hemorrhagic Shock Consensus Conference recommendations comments on practices that can be utilized in the prehospital setting including limitation of crystalloid resuscitation, consideration of blood product transfusion by emergency

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medical service (EMS) providers based on product availability, and the use of commercially available tourniquets by trained individuals in the setting of exsanguinating extremity hemorrhage.[8]

In traumatically injured children in hemorrhagic shock, the guidelines suggest prioritizing the use of blood products over the use of crystalloids for prehospital resuscitation.[9] Efforts to limit the use of crystalloids in children is supported in both national guidelines and recent literature. The most recent Advanced Trauma Life Saving Manual has changed its recommendations of two weight-based 20 milliliter per kilogram (mL/kg) crystalloid boluses in children to now a recommendation of one 20 mL/kg bolus of crystalloids prior to consideration of blood products.[10] Additional pediatric trauma studies suggest limiting the use of crystalloid boluses for children with hemorrhagic shock, as administering crystalloids in this population is associated with increased odds of mechanical ventilation, and longer intensive care unit and hospital stays.[11-13] There are several small observational or retrospective pediatric studies evaluating prehospital blood transfusion in the civilian and military settings. These studies have shown that this practice is feasible and safe. Despite limitations in sample size and inability to show mortality differences, these studies have demonstrated that prehospital transfusions results in less crystalloid administration, improved physiologic parameters at hospital arrival (including lactate, hemoglobin, and coagulation indices) with no differences in complications or other clinical outcomes.[14-16] A recently published study by Morgan et al. is the first study to show reduced 24-hour and in-hospital mortality for injured children who received blood transfusions in the prehospital setting close to their time of injury. From their 10 year retrospective cohort of over 14,000 pediatric trauma patients in a statewide trauma registry, 559 (4%) received a blood

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product transfusion, and 70 (0.5%) received a prehospital transfusion.[17] As expected, there were significant differences between patients receiving prehospital transfusions (PHT) and emergency department transfusions (EDT). To address potential selection bias, they developed a 3:1 propensity score match balancing appropriate confounders between patients in the PHT and EDT groups. This produced groups of 68 patients with PHT and 139 patients with EDT that were well balanced with regard to age, sex, race, mechanism of injury, shock index, prehospital Glasgow coma scale score (GCS), Injury Severity Score (ISS), and insurance type. After matching, both 24-hour (16% vs. 27%) and in-hospital mortality (20% vs. 32%) were lower in the PHT group. Finally, the authors utilized a mixed-effects logistic regression model, further adjusting for center-level effects, sex, insurance status, and ISS, which demonstrated a significantly lower risk of 24-hour and in-hospital mortality for recipients of prehospital transfusions. These data show that avoiding delays in transfusion by initiating resuscitation close to the time of injury may result in survival benefit.

Blood Product Resuscitation:

Component Transfusion of Pediatric Trauma Patients

The Pediatric Traumatic Hemorrhagic Shock Consensus Conference Guidelines also state that for traumatically injured children in hemorrhagic shock, blood products (blood components (RBCs plasma and platelets or low-titer group O whole blood) should be prioritized over crystalloid for in-hospital resuscitation.[9] When utilizing component products, attention should be placed on balanced transfusion of these products in high ratios to replace the patient's prior or ongoing blood loss. There are many military and civilian studies evaluating the best resuscitation strategies for pediatric trauma patients with specific evaluations focused on determining optimal

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ratios of component therapy **(Table 1)**. The largest retrospective review of the Trauma Quality Improvement Program (TQIP) data from 2017-2019 evaluated 583 massively transfused children. This study demonstrated the plasma/RBC ratio, as a continuous variable, was associated with improved 24 hour mortality (OR, 0.47; 95% CI, 0.28-0.80). In addition, those children transfused with a medium (≥1:2 and < 1:1) and high (≥ 1:1) plasma/RBC ratios has a 51% and 40% lower risk of death at 24 hours, respectively, compared to the low (<1:2) ratio group.[18] A smaller, retrospective study of five Level I pediatric trauma centers had similar findings in 110 pediatric trauma patients. In a logistic regression model, they demonstrated an increased mortality (OR, 3.08; 95% CI, 1.10-8.57) per unit increase over 1:1 ratio of RBC: plasma. Finally, in a multi-institutional, international, prospective observational study including 191 children with traumatic injury and life-threatening hemorrhage, there was an independent association with a plasma: RBC ratio of 1:2 with improved 24-hour survival (OR, 0.36; 95% CI, 0.13-0.99). This study also analyzed the plasma deficit (RBC ml/kg – plasma ml/kg) demonstrating an increased deficit was also associated with an increased 24 hour mortality (OR, 1.2; (95% CI, 1.05-1.3).[4] There have been additional publications that have not found an association between mortality and increased plasma/RBC ratios; however, these publications carry significant limitations to include lack of adjustment in their analyses, small sample sizes, and single center experiences. (**Table 1**)

Early utilization of platelets during trauma resuscitation seems practical in light of the laboratory data demonstrating that platelets may help repair the injured endothelium and emphasizing the importance of platelets in the milieu of hemostasis after trauma.[19, 20] However, many of the pediatric massive transfusion studies have failed to demonstrate an independent

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association between platelet: RBC ratios and improved clinical outcomes. The recent multi-institutional observational study in children with LTH did demonstrate that a platelet deficit (RBC ml/kg-platelet ml/kg) was independently associated with mortality at 24 hours (OR, 1.1; 95% CI, 1.05-1.2). However, in this same study, there was no survival advantage with the platelet/RBC ratio, though few children received high ratio platelet/RBC.[4] This finding suggests that deficits may more accurately reflect the lack of balance between platelets and RBCs compared to ratios, which do not account for the magnitude of the imbalance. A secondary analysis of the larger PROPPR trial that assessed the impact of platelet transfusions did show that the early use of platelets improved survival in adult patients who received a more balanced resuscitation.[21]

Use of Low Titer Whole Blood in Pediatric Trauma Patients

Another acceptable strategy for hemostatic resuscitation in children with traumatic LTH is utilization of low-titer group O whole blood (LTOWB). This product may offer several advantages, which include increased hemoglobin and platelet concentrations, and increased coagulation factors with approximately 33% less anticoagulants and preservatives compared to RBC, plasma and platelet units in a 1:1:1 unit ratio.[22] Utilization of LTOWB may lead to less dilutional coagulopathy, less hypocalcemia, and receipt of fewer blood products overall, which theoretically could reduce donor exposures and hemolytic reactions. In addition, due to the storage of LTOWB at 4°C, the platelets may be more hemostatic and there may be a lower risk of bacterial contamination than exists with the use of platelets stored at room temperature.[23] Finally, LTOWB provides a logistical advantage of only needing a single blood product that may be administered through a single access point, which may be advantageous in a pediatric patient

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with difficult or limited intravenous access. Although LTOWB use is less prevalent in pediatric trauma patients, the Pediatric Traumatic Hemorrhagic Shock Consensus Conference recommendations support consideration for using this product, when available, in the resuscitation of traumatically injured children in hemorrhagic shock.[9] There are at least 11 pediatric trauma centers in the US routinely using LTOWB for LTH. Studies evaluating the use of LTOWB in children demonstrate it more rapid and efficient transfusion, faster resolution of shock and coagulopathy[24], and less total blood products administered and mechanical ventilation days compared to component therapy.[25] While no study has shown a mortality benefit in all injured children, a recent single-center retrospective study evaluated the use of LTOWB in injured children requiring massive transfusion; after adjusting for appropriate confounders, LTOWB use as a part of the resuscitation was independently associated with improved 72 hour (aOR, 0.23; 95% CI, 0.08-0.70) and 28-day mortality (aOR, 0.41; 95% CI, 0.23-0.98).[26] **(Figure 1)**

Hemostatic adjuncts

Mechanical hemostatic adjuncts

Recent guidelines recommend the use of tourniquets in children with exsanguinating hemorrhage.[8] Multiple studies indicate the use of tourniquets in children decreases the volume of crystalloids given, transfusion requirements, and is associated with increased survival. There were no significant complications from tourniquet use.[27-32] Challenges with tourniquet use in children include overuse, improper application, and a need for more standardized training.[31]

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Topical hemostatic adjuncts

Topical adjuncts include fibrin and thrombin impregnated gauze and TXA soaked gauze. Though not specifically studied in pediatric trauma patients, these topical hemostatic adjuncts can be helpful in reducing bleeding in areas where packing with gauze is necessary.[33, 34]

Intravenous hemostatic adjuncts

The fibrinolytic pathway is an important contributor to traumatic coagulopathy. After injury, there is a complex interaction that occurs between the endothelium, platelets, and coagulation factors that results in thrombin generation and cross-linking of fibrin monomers. The aforementioned interaction results in the formation of a mature clot and seals the vascular injury at the injury site leading to hemostasis. Fibrinolysis is a physiologic process that occurs in parallel with fibrin cross-linking to prevent the extension of clotting beyond the site of injury. During injury, this fibrinolytic process can be physiologic or become pathologic to increased (hyperfibrinolysis) or reduced (fibrinolysis shutdown), both of which have been associated with increased mortality.[35]

Tranexamic acid (TXA), a lysine analog and a reversible inhibitor to the lysine receptor found on plasminogen, binds this receptor to prevent the binding of plasma and therefore blocking fibrinolysis. This hemostatic adjunct is well studied in the adult trauma population, but there is limited data in pediatric trauma patients. Prior to its wide use in the trauma setting, TXA has been widely utilized within the operative setting to decrease surgical bleeding in adult and pediatric patients undergoing surgery for spinal fusions, cranial vault remodeling, and cardiothoracic surgeries. These studies have all shown efficacy of TXA to decrease bleeding

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with a good safety profile.[36-39] Despite supportive literature for selective utilization of TXA in the adult trauma population, a survey of children's hospitals demonstrated limited use of TXA in pediatric trauma patients as only 7 of 46 centers included TXA in their massive transfusion protocols.[40]

The data evaluating the utilization of TXA in the pediatric trauma population is limited and studies have demonstrated mixed outcomes. A recent systematic literature review on this TXA utilization in pediatric trauma patients noted that TXA has a good safety profile, but evidence for improved outcomes was limited and strongest in the combat literature.[41] Since publication of the aforementioned review, the Massive Transfusion in Children (MATIC) trial prospectively evaluated pediatric resuscitation in patients with LTH in multiple centers in the US, Canada, and Italy.[4] In a secondary analysis, they evaluated the patients that received antifibrinolytics (TXA or epsilon-aminocaproic acid) during their resuscitation. In the antifibrinolyic group, there was significantly less 6-hour mortality (6% vs 17%; p=0.04) and less 6-hour mortality due to hemorrhage (4% vs. 14%; p=0.04). After adjusting for appropriate confounders (bleeding etiology, Pediatric Risk of Mortality score, age, and plasma deficit), the antifibrinolytic group had decreased 6- and 24-hour postbleed mortality. [42] **(Figure 2)** These data are limited by use of multiple antifibrinolytic agents, inclusion of children with medical and surgical bleeding etiology, and uncommon antifibrinolytic use. In addition, Gendler and colleagues have published the Israeli Defense Forces Medical Corps (IDF-MC) experience in utilization of pre-hospital TXA in pediatric trauma. From 2011 to 2021, 70 of 911 patients (<18 years of age) received TXA. Patients receiving TXA were more likely to suffer from shock, sustain more penetrating injuries, be treated with plasma or crystalloids, and undergo more

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lifesaving interventions. To control for these potential differences between TXA and non-TXA populations, they performed a 1:1 propensity score matching which failed to demonstrate an association between TXA use and lower odds of mortality.[43]

The current recommendations from the Pediatric Traumatic Hemorrhagic Shock Consensus Conference suggest the empiric use of tranexamic acid within 3 hours of injury might be considered.[9] Certainly, there are significant gaps in the research describing administration and outcomes of TXA use in pediatric trauma patients.

Intravenous hemostatic adjuncts also include coagulation factor concentrates such as rFVIIa, fibrinogen and prothrombin complex concentrates. While these agents are used by some practitioners, recent guidelines state there is insufficient evidence for the routine empiric use of these products due to insufficient evidence regarding their efficacy and safety.[9]

Cryoprecipitate may be an important hemostatic adjunct to consider since it includes fibrinogen, factors VIII, XIII, and VWF, which are important for fibrin formation, platelet adhesion and aggregation, in addition to reducing fibrinolysis. Few reports evaluating the use of cryoprecipitate in the resuscitation of injured children are published. The majority of our knowledge on this practice is extrapolated from adult data, suggesting that transfusion of cryoprecipitate to injured adults receiving massive transfusion is associated with a significantly lower mortality.[44] A recent propensity-weighted cohort study of the pediatric TQIP data found that giving cryoprecipitate within the first 4 hours of arrival was associated with lower 24-hour mortality compared to those that did not receive cryoprecipitate. The survival benefit associated

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with cryoprecipitate usage was lost overall for every subgroup by seven days, except for those with penetrating injuries and those who received an extremely massive transfusion (≥ 100 ml/kg).[44] An adjusted analysis from the MATIC dataset in of 449 children with LTH from all etiologies suggests that after Cox Hazard regression model generation controlling for PRISM score, bleeding etiology, age, sex, volume RBCs, volume platelets, antifibrinolytic use and cardiac arrest, cryoprecipitate use was independently associated with lower 24-hour mortality (OR (95% CI) = 0.46 (0.24-0.89), p=0.02) **(Figure 3)**.[45] Since the pediatric data on this is quite limited, future studies carefully evaluating cryoprecipitate and its contribution to overall resuscitation should be entertained.

The recent licensing of pathogen-reduced cryoprecipitate will allow for immediate availability since it can be stored at room temperature for 5 days, which will also reduce waste. In vitro data indicates this product has similar hemostatic effects compared to standard cryoprecipitate.[46] Clinical trials are needed to examine in vivo efficacy and safety.

Massive Transfusion Protocols

In severely injured pediatric trauma patients, it is recommended to begin an empiric hemostatic resuscitation using balanced blood component ratios or LTOWB in the framework of a massive transfusion protocol (MTP).[8] As noted in the introduction in order to take advantage of the MTP protocols, recognition of hemorrhagic shock and rapid activation of existing protocols is critical. Although there have been many studies evaluating massively transfused children, very few studies have evaluated the benefits of MTP implementation and use in children. Three single center, retrospective studies have evaluated the specific impact of implementation of MTPs on

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resuscitation outcomes in children.[47-49] The largest pediatric study from Hwu et al. compared 125 pre-MTP with 115 post-MTP implementation patients over a 10-year period. Although the post-MTP cohort was more severely injured, there was no difference in mortality between the two groups. Post-MTP patients received plasma and platelet transfusion earlier in the resuscitation and in a more balanced ratio with red blood cells.[49] Although the limited size of the population and the low mortality may preclude demonstrating a mortality difference, these studies suggest that MTPs are safe and may provide benefit in the resuscitation of severely injured pediatric trauma patients in hemorrhagic shock.

Practical Guide to Implementation of Damage Control Resuscitation Strategies for Pediatric Trauma Patients

The implementation of damage control resuscitation strategies for pediatric trauma patients will be a multidisciplinary effort that will require close collaboration between out of hospital emergency medical services, pediatric emergency medicine, pediatric critical care, pediatric lab medicine/pathology, pediatric surgery, and certainly other disciplines depending on the local landscape. First, summarizing and disseminating the literature and recommendations for damage control resuscitation in pediatric patients will establish common knowledge and understanding. A starting point within each organization may be to identify a dedicated and interested group of stakeholders. This group may then 1) establish the frequency and severity of children with traumatic hemorrhagic shock, local practice patterns and outcomes; 2) evaluate the institutions' or health systems' outcomes regarding pediatric trauma practices; 3) define the specific resources available at present; and 4) identify and prioritize areas for improvement, and 5) detail the immediate and future needs required to implement best practices.

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Specific areas trauma programs should consider evaluating include: use and indications for prehospital blood products, trauma team response times, the makeup of the trauma team, time from presentation to awareness of life threatening hemorrhage, time from awareness of life threatening hemorrhage to initiation of hemostatic resuscitation, frequency of MTP activation, and balance of resuscitation both with and without MTP activation. Review and revision of the MTP policy to incorporate recent data is essential. An often-overlooked aspect of MTP policies is the incorporation of frequent laboratory assessment to monitor for changes in metrics of oxygen delivery, hemostasis, calcium and potassium concentrations. Furthermore, once MTP guidelines are in place, regular educational programs with data-driven feedback to facilitate understanding and adherence is essential. This can include high fidelity simulations of the process to understand areas for improvement and post-hoc critical evaluation through a robust performance improvement process.

MTP Activation Teams

Similar to the development of cardiac arrest response teams and septic shock resuscitation teams, the concept of MTP activation teams have been developed. The goal of MTP activation teams is to incorporate additional clinical care team members in the resuscitation of a child with life threatening bleeding. In institutions where these have been established upon MTP activation for any etiology of bleeding the following team members arrive: surgeon (if not already present), pharmacist, and nursing leadership. The role of the surgeon is to assist the resuscitation team in determining if there is a surgical cause of bleeding and facilitating surgical control if it is present. The role of the pharmacist is to bring hemostatic adjuncts such as antifibrinolytics and calcium as well as remind the team to perform the laboratory measures that are part of the local MTP

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policy. Nursing leadership roles include assisting with the use or rapid infusers and blood warmers when needed. This is important since these devices are not frequently utilized in children's hospitals and not all staff will be familiar with their use when emergently needed. Nursing leadership will also provide bedside recording of all interventions and responses that occur during the MTP activation in the same manner that data is recorded with cardiac arrest teams. Nursing leadership also assists with facilitating the rapid transport of blood products from the blood bank if needed. These MTP activation teams provide additional support and provides standardization and data recording which can be very helpful with the review of performance of these high risk and low frequency events.

Limitations for Implementing Hemostatic Resuscitation Practices

The main limitation for implementing hemostatic resuscitation principles is the lack of high quality data that establishes efficacy and safety. The upcoming MATIC-2 trial, a multicenter adaptive platform trial, is designed to provide some of this well needed data. This study will examine the effects of LTOWB compared to components and TXA compared to placebo in children with life threatening traumatic injury requiring massive transfusion. It will include up to 1000 children at 20 centers across the United States. As a platform trial, it can eventually include other interventions such as cryoprecipitate, prothrombin complex concentrate, or other hemostatic adjuncts. This trial will also include mechanistic studies utilizing a robust multi-OMICS analysis that can not only define mechanisms of TIC in children, but also determine if there are patient subgroups that respond more favorably to one therapy or another.

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Another limitation is the lack of quality data to aid in recognition of LTH and establish indications for when DCR therapies should be initiated. Studies are being developed to utilize computational biology and machine learning to establish more objective measures of when certain therapies are indicated.

A limitation to the more widespread use of LTOWB is the availability of RhD- LTOWB. The use of RHD- LTOWB is advantageous in girls before RHD type is known to prevent the risk of a potential future complication of hemolytic disease of the fetus and newborn (HDFN). The risk of any degree of HDFN after receipt of RhD+ blood products has been simulated to be 0-6% with a 0.3% risk of fetal death and is contingent on a number of factors (**Figure 4**).[50, 51] While RhD- LTOWB avoids this risk entirely, it is in very short supply; only 6% of the population is able to donate RhD- LTOWB. In practice, some centers utilize RhD+ LTOWB in females of childbearing potential acknowledging this risk of HDFN as well as the described benefits of LTOWB; of the 11 programs using LTOWB in pediatric patients, 6 of them will use RhD+ LTOWB if needed. However, some adult and pediatric centers exclude FCPs from receipt of LTOWB entirely. Multiple surveys have been performed to incorporate the patients' view of the risk/benefit assessment of using RhD+ LTOWB for life threatening bleeding. When presented with a 0-6% risk of HDFN and a 2-4% improvement in survival with use of LTOWB, women, their partners, and parents of young girls overwhelmingly state they would accept RhD+ LTOWB.[52, 53] Input from key stakeholders to include patient or family advocates as well as RCT level evidence to assess the impact of LTOWB will further inform these challenging decisions.

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Conclusions

From a clinical perspective, well-designed prospective clinical trials to evaluate the mechanisms of TIC and outcomes of pediatric patients resuscitated with all aspects of hemostatic resuscitation are needed. Appropriate modeling of prehospital data elements to improve recognition and expedite treatment of hemorrhagic shock in children should be prioritized. From a system/programmatic perspective, defining, standardizing, and improving collection of common data elements needed for pediatric trauma research should be a high priority. This should include placing importance on capturing time-sensitive elements in the pre-hospital and hospital setting which may help us better understand the dynamics, circumstances, and indications for DCR therapies in children with life threatening bleeding from traumatic injury.

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References

1. Holcomb JB, Jenkins D, Rhee P, Johannigman J, Mahoney P, Mehta S, et al. Damage control resuscitation: directly addressing the early coagulopathy of trauma. *J Trauma*. 2007;62(2):307-10.
2. Spinella PC. Zero preventable deaths after traumatic injury: An achievable goal. *J Trauma Acute Care Surg*. 2017;82(6S Suppl 1):S2-s8.
3. Shroyer MC, Griffin RL, Mortellaro VE, Russell RT. Massive transfusion in pediatric trauma: analysis of the National Trauma Databank. *J Surg Res*. 2017;208:166-72.
4. Leonard JC, Josephson CD, Luther JF, Wisniewski SR, Allen C, Chiusolo F, et al. Life-Threatening Bleeding in Children: A Prospective Observational Study. *Crit Care Med*. 2021;49(11):1943-54.
5. Acosta JA, Yang JC, Winchell RJ, Simons RK, Fortlage DA, Hollingsworth-Fridlund P, et al. Lethal injuries and time to death in a level I trauma center. *J Am Coll Surg*. 1998;186(5):528-33.
6. Sullivan TM, Gestrich-Thompson WV, Milestone ZP, Burd RS. Time is tissue: Barriers to timely transfusion after pediatric injury. *J Trauma Acute Care Surg*. 2023;94(1S Suppl 1):S22-s8.
7. Alberto EC, Mastrianni A, Sullivan TM, McCarthy KH, Milestone ZP, Chung L, et al. Factors Affecting Peripheral Intravenous Catheter Placement During Pediatric Trauma Resuscitation. *J Surg Res*. 2023;283:241-8.
8. Russell RT, Esparaz JR, Beckwith MA, Abraham PJ, Bembea MM, Borgman MA, et al. Pediatric traumatic hemorrhagic shock consensus conference recommendations. *J Trauma Acute Care Surg*. 2023;94(1S Suppl 1):S2-s10.

ACCEPTED

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9. Russell RT, Esparaz JR, Beckwith MA, Abraham PJ, Bembea MM, et al. Pediatric Trauma Hemorrhagic Shock Consensus Conference Recommendations. *J Trauma Acute Care Surg*. 2023.

10. Trauma ACoSCo. Advanced Trauma Life Support (ATLS) student manual. Surgeons ACo, editor. Chicago, IL2018.

11. Polites SF, Moody S, Williams RF, Kayton ML, Alberto EC, Burd RS, et al. Timing and volume of crystalloid and blood products in pediatric trauma: An Eastern Association for the Surgery of Trauma multicenter prospective observational study. *J Trauma Acute Care Surg*. 2020;89(1):36-42.

12. Polites SF, Nygaard RM, Reddy PN, Zielinski MD, Richardson CJ, Elsbernd TA, et al. Multicenter study of crystalloid boluses and transfusion in pediatric trauma-When to go to blood? *J Trauma Acute Care Surg*. 2018;85(1):108-12.

13. Schauer SG, April MD, Becker TE, Cap AP, Borgman MA. High crystalloid volumes negate benefit of hemostatic resuscitation in pediatric wartime trauma casualties. *J Trauma Acute Care Surg*. 2020;89(2S Suppl 2):S185-s91.

14. Potter DD, Berns KS, Elsbernd TA, Zietlow SP. Prehospital use of blood and plasma in pediatric trauma patients. *Air Med J*. 2015;34(1):40-3.

15. Van Dijck CP, Stansbury LG, Latimer AJ, Butler EK, Nathwani R, Wall J, et al. Hemostatic Resuscitation of Pediatric Trauma Patients During Air Medical Transport: A Retrospective Matched Cohort Study. *Air Med J*. 2021;40(5):344-9.

16. Shirek G, Phillips R, Shahi N, Pickett K, Meier M, Recicar J, et al. To give or not to give? Blood for pediatric trauma patients prior to pediatric trauma center arrival. *Pediatr Surg Int*. 2022;38(2):285-93.

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17. Morgan KM, Abou-Khalil E, Strotmeyer S, Richardson WM, Gaines BA, Leeper C. When Minutes Matter: Prehospital Transfusion Reduces Mortality in Pediatric Trauma. *JAMA Pediatr*. 2023.

18. Butler EK, Mills BM, Arbabi S, Bulger EM, Vavilala MS, Groner JI, et al. Association of Blood Component Ratios With 24-Hour Mortality in Injured Children Receiving Massive Transfusion. *Crit Care Med*. 2019;47(7):975-83.

19. Trivedi A, Potter DR, Miyazawa BY, Lin M, Vivona LR, Khakoo MA, et al. Freeze-dried platelets promote clot formation, attenuate endothelial cell permeability, and decrease pulmonary vascular leak in a murine model of hemorrhagic shock. *J Trauma Acute Care Surg*. 2021;90(2):203-14.

20. Baimukanova G, Miyazawa B, Potter DR, Muench MO, Bruhn R, Gibb SL, et al. Platelets regulate vascular endothelial stability: assessing the storage lesion and donor variability of apheresis platelets. *Transfusion*. 2016;56 Suppl 1(Suppl 1):S65-75.

21. Cardenas JC, Zhang X, Fox EE, Cotton BA, Hess JR, Schreiber MA, et al. Platelet transfusions improve hemostasis and survival in a substudy of the prospective, randomized PROPPR trial. *Blood Adv*. 2018;2(14):1696-704.

22. Leeper CM, Yazer MH, Neal MD. Whole-Blood Resuscitation of Injured Patients: Innovating from the Past. *JAMA Surg*. 2020;155(8):771-2.

23. Kahn RA, Syring RL. The fate of bacteria introduced into whole blood from which platelet concentrates were prepared and stored at 22 or 4C. *Transfusion*. 1975;15(4):363-7.

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24. Leeper CM, Yazer MH, Triulzi DJ, Neal MD, Gaines BA. Whole Blood is Superior to Component Transfusion for Injured Children: A Propensity Matched Analysis. *Ann Surg*. 2020;272(4):590-4.

25. Anand T, Obaid O, Nelson A, Chehab M, Ditillo M, Hammad A, et al. Whole blood hemostatic resuscitation in pediatric trauma: A nationwide propensity-matched analysis. *J Trauma Acute Care Surg*. 2021;91(4):573-8.

26. Gaines BA, Yazer MH, Triulzi DJ, Sperry JL, Neal MD, Billiar TR, et al. Low Titer Group O Whole Blood In Injured Children Requiring Massive Transfusion. *Ann Surg*. 2023;277(4):e919-e24.

27. Kragh JF, Jr., Cooper A, Aden JK, Dubick MA, Baer DG, Wade CE, et al. Survey of trauma registry data on tourniquet use in pediatric war casualties. *Pediatr Emerg Care*. 2012;28(12):1361-5.

28. Kragh JF, Jr., Walters TJ, Baer DG, Fox CJ, Wade CE, Salinas J, et al. Survival with emergency tourniquet use to stop bleeding in major limb trauma. *Ann Surg*. 2009;249(1):1-7.

29. Kragh JF, Jr., Littrel ML, Jones JA, Walters TJ, Baer DG, Wade CE, et al. Battle casualty survival with emergency tourniquet use to stop limb bleeding. *J Emerg Med*. 2011;41(6):590-7.

30. Kragh JF, Jr., Nam JJ, Berry KA, Mase VJ, Jr., Aden JK, 3rd, Walters TJ, et al. Transfusion for shock in US military war casualties with and without tourniquet use. *Ann Emerg Med*. 2015;65(3):290-6.

ACCEPTED

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31. Sokol KK, Black GE, Azarow KS, Long W, Martin MJ, Eckert MJ. Prehospital interventions in severely injured pediatric patients: Rethinking the ABCs. *J Trauma Acute Care Surg*. 2015;79(6):983-9; discussion 9-90.

32. Ode G, Studnek J, Seymour R, Bosse MJ, Hsu JR. Emergency tourniquets for civilians: Can military lessons in extremity hemorrhage be translated? *J Trauma Acute Care Surg*. 2015;79(4):586-91.

33. Boccio E, Hultz K, Wong AH. Topical Tranexamic Acid for Hemostasis of an Oral Bleed in a Patient on a Direct Oral Anticoagulant. *Clin Pract Cases Emerg Med*. 2020;4(2):146-9.

34. Peng HT. Hemostatic agents for prehospital hemorrhage control: a narrative review. *Mil Med Res*. 2020;7(1):13.

35. Borgman MA, Nishijima DK. Tranexamic acid in pediatric hemorrhagic trauma. *J Trauma Acute Care Surg*. 2023;94(1S Suppl 1):S36-s40.

36. Sethna NF, Zurakowski D, Brustowicz RM, Bacsik J, Sullivan LJ, Shapiro F. Tranexamic acid reduces intraoperative blood loss in pediatric patients undergoing scoliosis surgery. *Anesthesiology*. 2005;102(4):727-32.

37. Goobie SM, Meier PM, Pereira LM, McGowan FX, Prescilla RP, Scharp LA, et al. Efficacy of tranexamic acid in pediatric craniosynostosis surgery: a double-blind, placebo-controlled trial. *Anesthesiology*. 2011;114(4):862-71.

38. Dadure C, Sauter M, Bringuier S, Bigorre M, Raux O, Rochette A, et al. Intraoperative tranexamic acid reduces blood transfusion in children undergoing craniosynostosis surgery: a randomized double-blind study. *Anesthesiology*. 2011;114(4):856-61.

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39. Giordano R, Palma G, Poli V, Palumbo S, Russolillo V, Cioffi S, et al. Tranexamic acid therapy in pediatric cardiac surgery: a single-center study. *Ann Thorac Surg*. 2012;94(4):1302-6.

40. Horst J, Leonard JC, Vogel A, Jacobs R, Spinella PC. A survey of US and Canadian hospitals' paediatric massive transfusion protocol policies. *Transfus Med*. 2016;26(1):49-56.

41. Kornelsen E, Kuppermann N, Nishijima DK, Ren LY, Rumantir M, Gill PJ, et al. Effectiveness and safety of tranexamic acid in pediatric trauma: A systematic review and meta-analysis. *Am J Emerg Med*. 2022;55:103-10.

42. Spinella PC, Leonard JC, Gaines BA, Luther JF, Wisniewski SR, Josephson CD, et al. Use of Antifibrinolytics in Pediatric Life-Threatening Hemorrhage: A Prospective Observational Multicenter Study. *Crit Care Med*. 2022;50(4):e382-e92.

43. Gendler S, Gelikas S, Talmy T, Lipsky AM, Avital G, Nadler R, et al. Prehospital Tranexamic Acid Administration in Pediatric Trauma Patients: A Propensity-Matched Analysis of the Israeli Defense Forces Registry. *Pediatr Crit Care Med*. 2023.

44. Ditillo M, Hanna K, Castanon L, Zeeshan M, Kulvatunyou N, Tang A, et al. The role of cryoprecipitate in massively transfused patients: Results from the Trauma Quality Improvement Program database may change your mind. *J Trauma Acute Care Surg*. 2020;89(2):336-43.

45. Horst JA, Spinella PC, Leonard JC, Josephson CD, Leeper CM. Cryoprecipitate for the treatment of life-threatening hemorrhage in children. *Transfusion*. 2023.

ACCEPTED

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46. Thomas KA, Shea SM, Spinella PC. Effects of pathogen reduction technology and storage duration on the ability of cryoprecipitate to rescue induced coagulopathies in vitro. *Transfusion*. 2021;61(6):1943-54.

47. Chidester SJ, Williams N, Wang W, Groner JI. A pediatric massive transfusion protocol. *J Trauma Acute Care Surg*. 2012;73(5):1273-7.

48. Hendrickson JE, Shaz BH, Pereira G, Parker PM, Jessup P, Atwell F, et al. Implementation of a pediatric trauma massive transfusion protocol: one institution's experience. *Transfusion*. 2012;52(6):1228-36.

49. Hwu RS, Spinella PC, Keller MS, Baker D, Wallendorf M, Leonard JC. The effect of massive transfusion protocol implementation on pediatric trauma care. *Transfusion*. 2016;56(11):2712-9.

50. Seheult JN, Stram MN, Pearce T, Bub CB, Emery SP, Kutner J, et al. The risk to future pregnancies of transfusing Rh(D)-negative females of childbearing potential with Rh(D)-positive red blood cells during trauma resuscitation is dependent on their age at transfusion. *Vox Sang*. 2021;116(7):831-40.

51. Yazer MH, Díaz-Valdés JR, Triulzi DJ, Spinella PC, Emery SP, Young PP, et al. Considering equality in transfusion medicine practice. *Br J Haematol*. 2023.

52. Yu G, Siegler J, Hayes J, Yazer MH, Spinella PC. Attitudes of American adult women toward accepting RhD-mismatched transfusions in bleeding emergencies. *Transfusion*. 2022;62 Suppl 1:S211-s7.

53. Morgan KM, Lobo R, Annen K, Villarreal RI, Chou S, Uter S, et al. Parent perceptions of emergent blood transfusion in children. *Transfusion*. 2023;63 Suppl 3:S35-s45.

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FIGURE LEGENDS

Figure 1: Children who received LTOWB as part of their resuscitation had significantly decreased mortality at both 72 hours and 28 days post-trauma (AOR 0.23, p=0.009 and AOR 0.41, p=0.02, respectively); LTOWB: low titer group O whole blood. Reproduced with permission from Gaines et al. (Reference #26).

Figure 2: Resuscitation with antifibrinolytics is associated with an improved 6-hour (p=0.04) mortality and approached significance for improved 24-hour mortality (p=0.08) on unadjusted analysis compared with resuscitation without antifibrinolytics. Both 6-hour (p=0.04) and 24-hour (p=0.04) survivals were improved after adjusting for PRISM, etiology of bleed, age, and plasma deficit. PRISM: Pediatric Risk of Mortality Score. *Reproduced with permission from Spinella et al.*(Reference # 42).

Figure 3: After Cox hazard regression model generation controlling for PRISM score, bleeding etiology, age, sex, volume of RBC's, volume platelets, antifibrinolytic use and cardiac arrest, cryoprecipitate administration was independently associated with lower 6-hour mortality, HR (95% CI), 0.41 (0.19-0.89), (p=0.02) and 24-hour mortality, HR (95% CI), 0.46 (0.24-0.89), (p=0.02). PRISM: Pediatric Risk of Mortality Score, HR: hazards ratio. Reproduced with permission from Horst et al. (Reference # 45).

Figure 4: Swiss cheese model depicting all of the steps that must occur from the time that a woman is transfused with RhD-positive red blood cells (RBC) or low titer group O whole blood

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(LTOWB) during trauma resuscitation until a future fetus might potentially experience a perinatal adverse event from hemolytic disease of the fetus and newborn (HFDN); similarly, if only one of these variables occurs, a future fetus would also not be at risk for HFDN. *Reproduced with permission from Yazer et al.* (Reference #51).

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Figure 1

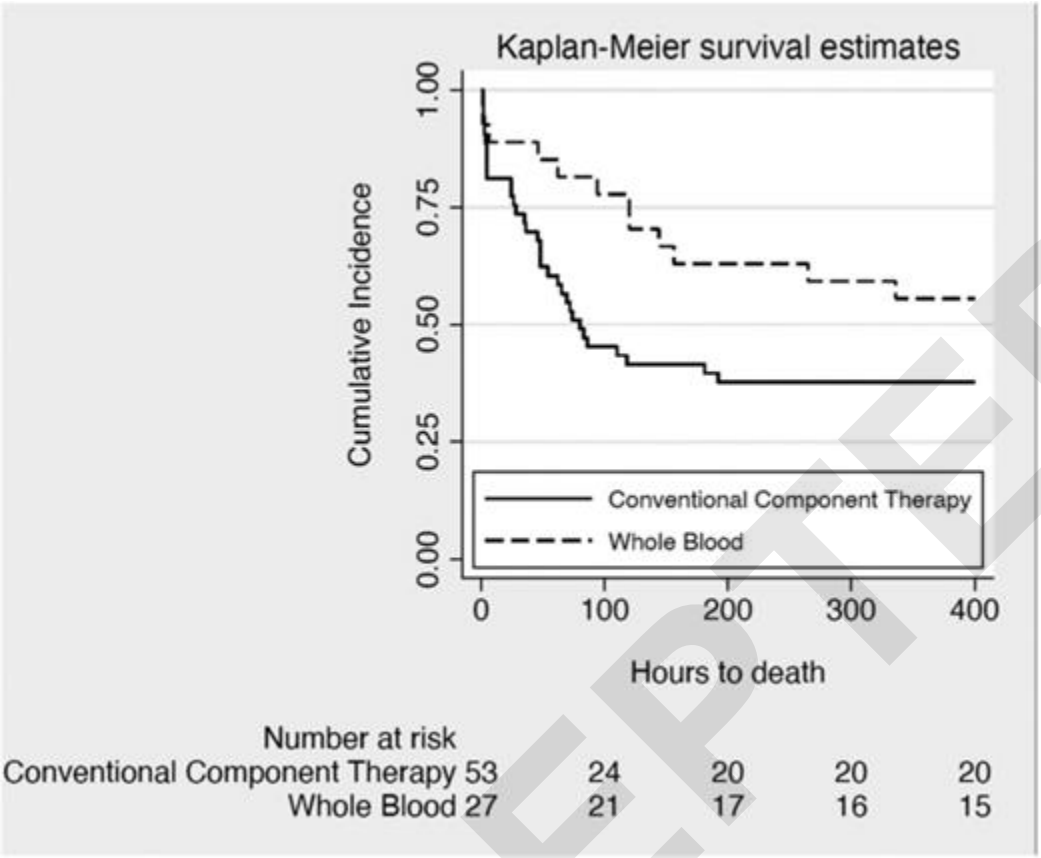

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Figure 2

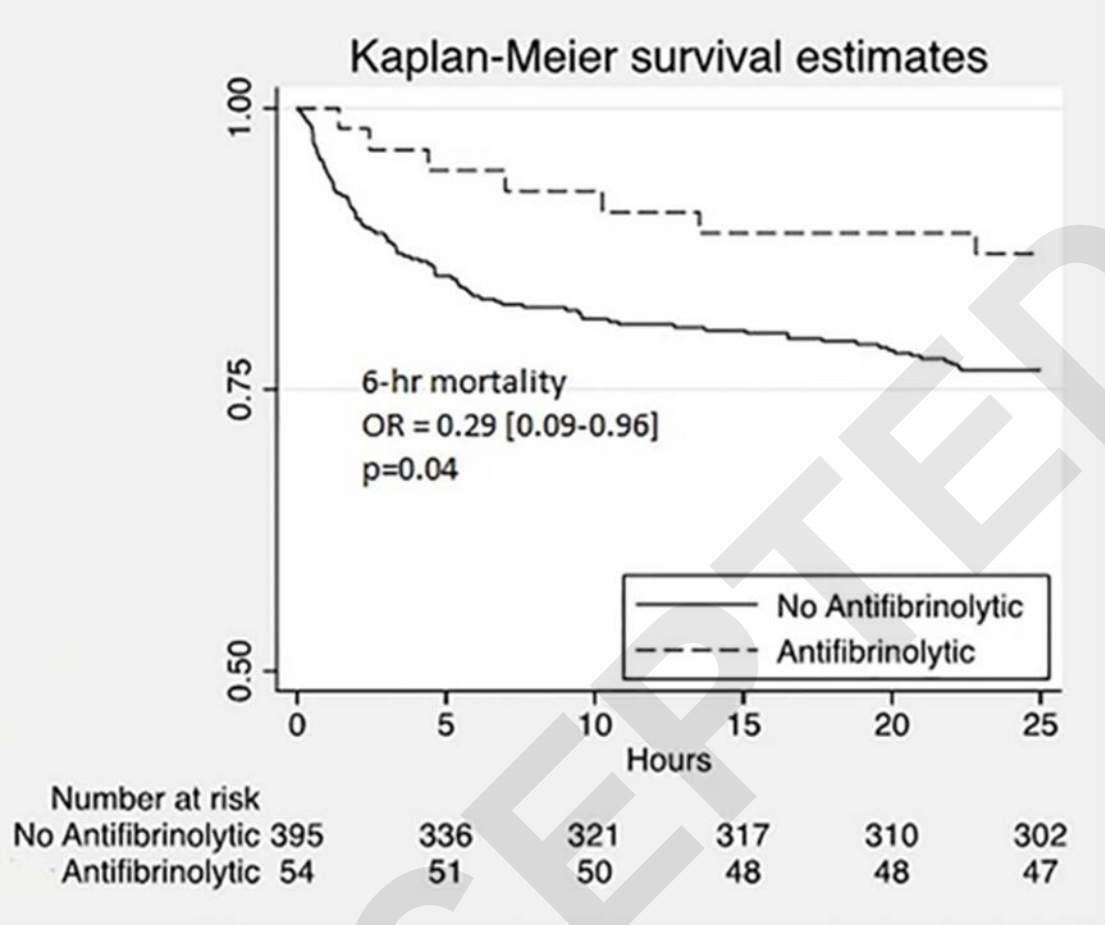

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Figure 3

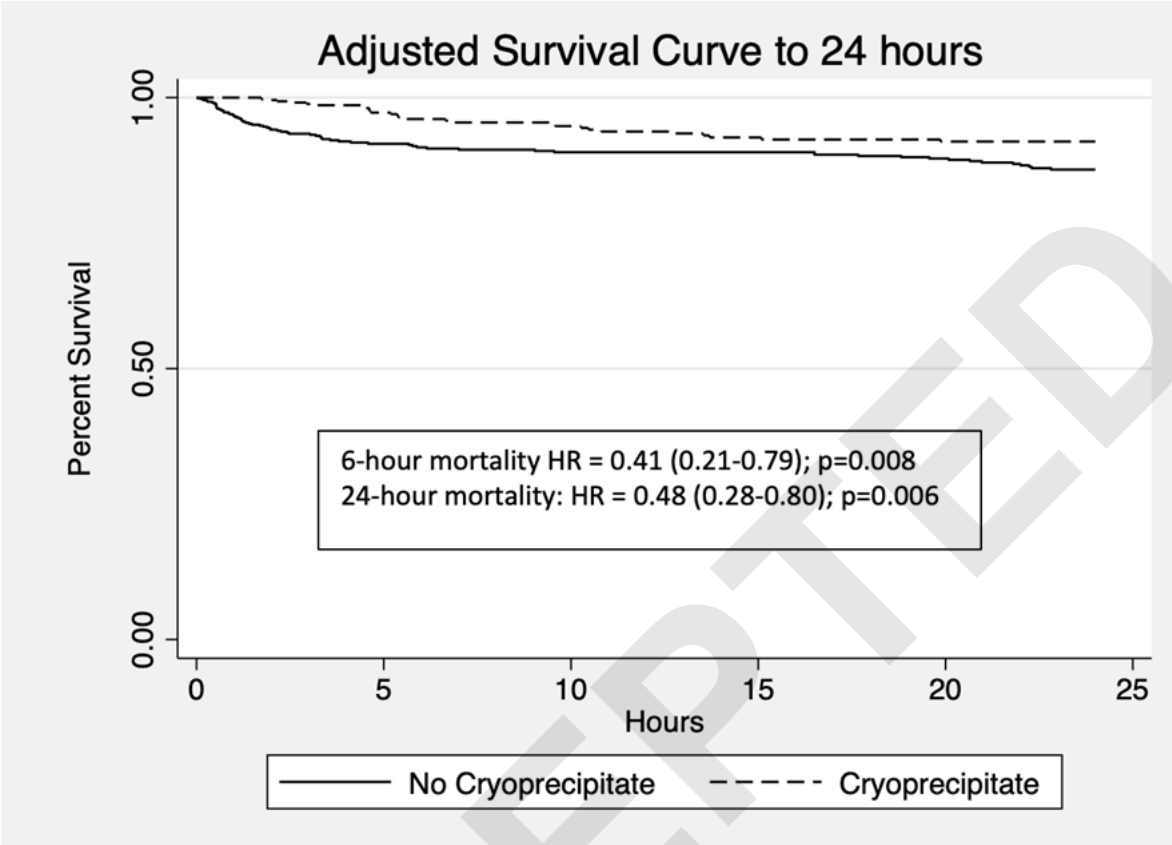

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Figure 4

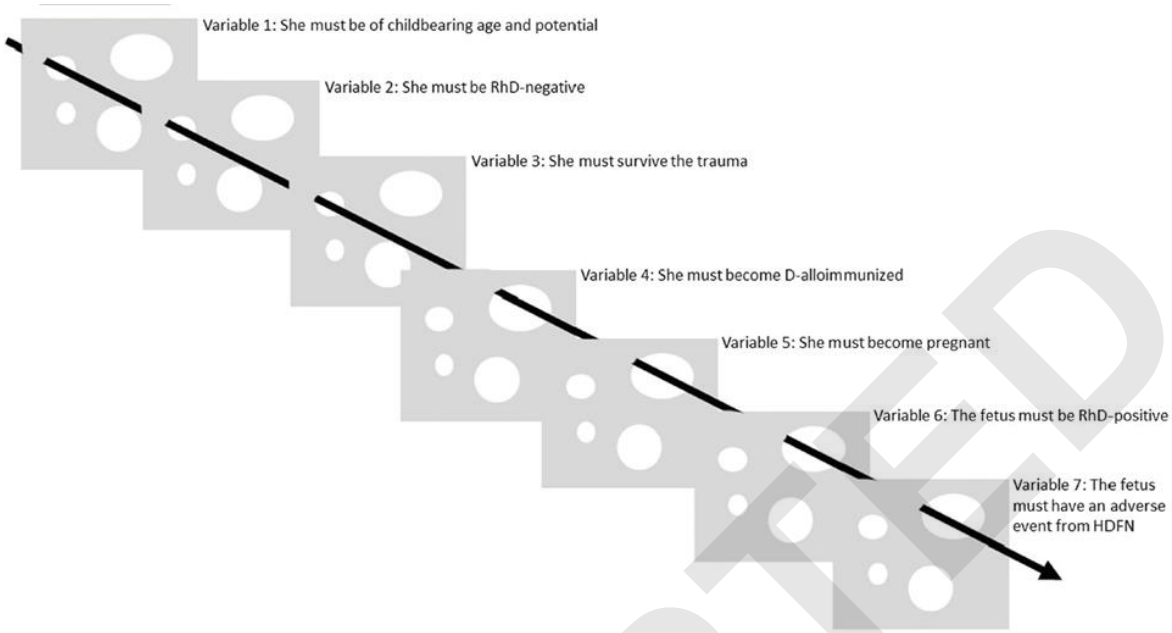

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Table 1. Literature evaluating transfusion ratios in hemostatic resuscitation in children

Publication year	1st author	Study design	Setting	Sample size (n)	Population	Age ±SD or Median(IQR)	ISS	Intervention ± comparator	Blood products given	Primary outcome	Conclusion
2019	Cunningham	Retro-spective cohort	Trauma centers (TQIP)	465	Blunt / penetrating trauma	8 yr (2-15)	Mean 34 [25-34]	High or medium plasma/RBC ratio (≥ 1:1, ≥ 1:2 or < 1:1) vs. low (< 1:2)	MT of plasma & RBC	Blood product volume in 24 h.	Blood product volume in 24 h: greatest with medium plasma:RBC ratio (90 [56-164]) mL/kg; P < 0.01). Survival: better with high plasma:RBC ratio (P = 0.02).
2019	Butler	Retro-spective cohort	Trauma Centers (TQIP)	583	Blunt / penetrating trauma, gunshot / stab wound, other	5 yr (2-10)	Mean 29	High or medium plasma/RBC ratio (≥ 1:1, ≥ 1:2 or < 1:1) vs. low (< 1:2)	MT of plasma & RBC	Mortality (19.7%)	Risk of death: high versus low plasma/RBC ratio: • High ratio (≥ 1:1): 51% lower (aRR, 0.49; 95% CI, 0.27–0.87; p = 0.02). • Medium ratio (≥ 1:2 and < 1:1): 40% lower (aRR, 0.60; 95% CI, 0.39–0.92; p = 0.02).
2017	Cannon	Retro-spective cohort	Military trauma/DOD	364	Blunt / penetrating trauma, other	8 yr (4-12)	Mean 17	High (> 1:2) vs. low (< 1:2) plasma/RBC ratio	MT of plasma & RBC	Mortality at 24 hr (18.7%)	No difference in all-cause mortality at 24 hours (high, 8.0% vs low, 9.2%; p = 0.75) and hospital discharge (high, 17.1% vs. low 21.5%; p = 0.39). Regression analysis demonstrated no associated mortality benefit with a high ratio (hazards ratio, 2.04; 95% confidence interval, 0.48-8.73; p = 0.34).
2021	Leonard	Prospective Observational	PICU population with LTB	449 (n=207 trauma)	Trauma, operative, and medical bleeding	10.4 yr (4.7-15.4)	29 (20-38)	MT	Plasma, PLT, RBC	6h, 24h, and 28 day mortality	35.7% of death occurred during MT (40.5% trauma); 6 hour trauma mortality: 63% bleeding, 37% CNS injury; 24 hour trauma mortality: 56% bleeding, 42% CNS injury; 28 day trauma mortality: 58% CNS injury
2018	Noland	Multicenter Retrospective cohort	Five Level 1 pediatric trauma centers	110	Blunt/ penetrating trauma	5.9 yr (3-11.4)	26 (20-37)	RBC: FFP ratio--1:1, 2:1. and 3:1 or greater	Plasma, PLT, RBC	Survival	RBC:FFP ratio of 1:1 was associated with highest survival in patients receiving MT. Ratios of 2:1 or ≥3:1 associated with increased risk of mortality
2017	Hwu	Retro-spective cohort	ER	38	Blunt / penetrating trauma	6.0 yr (2.8-14.9)	Mean 33	High (≥1:2) vs. low (<1:2) plasma: RBC (P:R) ratios	MT of plasma & RBC	In-hospital mortality (45.8%)	No significant difference in in-hospital mortality (45.8% vs. 64.3%) between high and low P: R ratio at 24 h from

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											injury.
2020	Schauer	Retrospective	Military Trauma (DOD)	521	Penetrating. Explosive, Blunt trauma	10 yr (5-13)	17 (13-25)	Large crystalloid administration effect on high (>1:2; FFP:PRBC) vs. low ≤1:2;FFP:PRBC) ratio	Plasma, PLT, RBC,	In-hospital survival	Association with survival in MT pediatric trauma patients who received a high Plasma/PRBC ratio and low crystalloid volume <40 ml/kg); Benefit of survival in high ratio group is negated in those receiving high crystalloid volume

[a] Mean ±SD, median and interquartile range (IQR: 25th and 75th quartile) or proportion (%).

Abbreviations: TQIP: Trauma Quality Improvement Program; yr: years; MT: massive transfusion; PLT: platelets; RBC: packed red blood cells; ICU: Intensive Care Unit; aRR: adjusted RR; FFP: fresh frozen plasma; INR: international normalized ratio; IQR: interquartile range (25th and 75th quartile); ISS: injury severity score; LOS: length of stay; ER: Emergency Room; DOD: Department of Defense; LTB: Life-threatening bleeding; mo: month; mod: moderate; MTP: MT protocol; NR: not reported. OR: odds ratio; CT: component therapy;

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