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Pediatric Traumatic Hemorrhagic Shock Consensus Conference Recommendations

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Media Summary: Hemorrhagic shock remains a preventable cause of death in pediatric trauma patients. Based on systematic literature reviews, this manuscript discusses clinical recommendations, expert consensus statements, and good practice statements for the care of pediatric patients in traumatic hemorrhagic shock.

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Summary

Hemorrhagic shock in pediatric trauma patients remains a challenging, yet preventable cause of death. There is little high-quality evidence available to guide specific aspects of hemorrhage control and specific resuscitation practices in this population. We sought to generate clinical recommendations, expert consensus and good practice statements to aid providers in care for these difficult patients.

The Pediatric Traumatic Hemorrhagic Shock Consensus Conference (PTHSCC) process included systematic reviews related to six subtopics and one consensus meeting. A panel of 16 consensus multidisciplinary committee members evaluated the literature related to six specific topics: 1) blood products and fluid resuscitation for hemostatic resuscitation, 2) utilization of pre-hospital blood products, 3) use of hemostatic adjuncts, 4) tourniquet use, 5) pre-hospital airway and blood pressure management, 6) conventional coagulation tests or thromboelastography-guided resuscitation.

A total of 21 recommendations are detailed in this manuscript: 2 clinical recommendations, 14 expert consensus statements and 5 good practice statements. The statement, the panel's voting outcome, the rationale for each statement intend to give pediatric trauma providers the latest evidence and guidance to care for pediatric trauma patients experiencing hemorrhagic shock.

With a broad multidisciplinary representation, the PTHSCC systematically evaluated the literature, developed clinical recommendations, expert consensus and good practice statements concerning topics in traumatically injured pediatric patients with hemorrhagic shock.

Level of Evidence: N/A

Keywords: trauma, pediatrics, hemorrhage, consensus

Introduction

Trauma is the leading cause of pediatric mortality, potential years of life lost, and a significant medical cost in the developed world.[1, 2] Thirty day mortality in children with traumatic hemorrhagic shock is 36-50% compared to 20-25% reported in adults.[3, 4] An estimated 1,000-2,000 preventable traumatic deaths in children per year after injury occur in the United States due to inadequate or delayed care.[5] Recent retrospective and prospective observational studies indicate that transfusion strategies (limiting crystalloid, appropriate transfusion ratios, and use of whole blood) and intravenous hemostatic adjunct therapies can reduce morbidity and mortality in children with traumatic hemorrhagic shock.[6-9] For this reason, hemostatic strategies represent a key target for standardization and subsequent investigation. However due to the lack of high-quality clinical trials to guide practice, hemostatic resuscitation strategies and the utilization of global assays of hemostasis for goal directed therapy are highly variable across sites.[10, 11] There is also a lack of agreement upon critical definitions of pediatric massive transfusion, definition of coagulopathy and critical common data elements required for clinical trial design. To address these challenges, we organized a multidisciplinary team of experts and key stakeholders to: 1) develop consensus statements on best practice in resuscitation strategies for pediatric trauma patients experiencing hemorrhagic shock based on the current literature, 2) create a strategy, in collaboration with implementation experts, for adaptive dissemination and implementation into clinical and research environments, and 3) develop future research priorities for studying resuscitation practices for pediatric traumatic hemorrhagic shock and foster collaboration in pursuit of improved clinical care for these patients.

Methods

The methodology for the Pediatric Traumatic Hemorrhagic Shock Consensus Conference (PTHSCC) follow the standards set by the Institute of Medicine for developing comprehensive evidence-based recommendations. When evidence was lacking, the panel developed expert consensus statements and good practice statements for decision making in pediatric trauma patients experiencing hemorrhagic shock. The complete methods are in **Appendix A**, http://links.lww.com/TA/C726, and the good practice statements in **Appendix B**, http://links.lww.com/TA/C727**.**

Clinical Recommendations (n=2) and Expert Consensus Statements (n= 14):

1) Blood products and fluid resuscitation in pediatric traumatic hemorrhagic shock

1.1: In traumatically injured children in hemorrhagic shock, we suggest prioritizing the use of blood products over the use of crystalloids for resuscitation. *Consensus Panel Expertise, 100% agreement (n=16), median 9, IQR: 8-9.*

Rationale: During and after the Vietnam War, crystalloids and colloids replaced blood as the primary initial resuscitative solution for hemorrhagic shock. This change was in part due to logistic difficulties of using blood and the infectious disease risks of blood products. The shift to crystalloids was supported by research performed by Carrico et al. indicating that the interstitial compartment or "third space" needed to be resuscitated with 1 to 2 liters of crystalloids to perfuse the tissues. This research further recommended that the transfusion of whole blood (WB) would only be indicated if hemodynamic instability persisted following administration of crystalloids.[12] To the detriment of patients with severe bleeding, misinterpretation of these data contributed to overuse of crystalloids before any blood product were administered. When used in practice, this approach could result in dilutional coagulopathy and severe interstitial edema. A shift from early blood product administration to a preference for early crystalloid and colloid use led to an increase in acute respiratory distress syndrome, abdominal compartment syndrome, multiorgan failure, and anasarca in intensive care units (ICUs).[13]

These outcomes were predicted by Shoemaker in 1976[14] when he challenged the notion that the interstitial compartment required resuscitation. He instead emphasized the need for whole blood (WB) to treat significant bleeding when the hematocrit fell below 30%. The overuse of crystalloids continued despite a call for changes in practice recommended by Moore and Shires as early as 1967. In an editorial, Moore and Shires state, “blood should still be replaced during major operative surgery as it is lost. The use of balanced salt solutions appears to be a physiological adjunct to surgical trauma, not a substitute for blood.” Subsequent research has demonstrated that a crystalloid-based resuscitation strategy leads to higher inflammation and vascular permeability compared to WB.[14]

Data supporting the use of blood products instead of crystalloids in children include a multicenter prospective observational study performed from April 2018 to Sept 2019.[15] In this study of 712 children from 24 trauma centers, each crystalloid bolus after the first was incrementally associated with an increased odds of more mechanical ventilation and intensive care unit days and longer hospital stays. A longer time to initiate the first transfusion was also associated with more mechanical ventilation days. In another retrospective study of 512 children admitted to combat support hospitals between 2007 and 2016, the authors evaluated the association of high crystalloid use (> 40ml/kg in 24 hours) for patients receiving high or low plasma:RBC ratios (1:2 threshold).[16] In children who received a high ratio of plasma:RBCs and low crystalloid volume, there was an independent association with improved survival (odds ratio [OR] 3.42; 95% confidence interval [CI], 1.04-11.24). In contrast, children with a high ratio of plasma:RBCs with high crystalloid volumes was not associated with improved survival (OR 0.61; [0.28-1.29]). The authors concluded that the high crystalloid volume negated the potential survival benefit of high plasma:RBC ratios in children with severe traumatic bleeding.

A secondary analysis of the PAMPer trial showed similar findings. This study of injured adults compared four groups of patients based on prehospital resuscitation with PRBC and plasma, plasma only, PRBC only, and crystalloid only. For patients with severe traumatic bleeding, they found that the exclusive use of crystalloids worsened survival compared to the partial use of blood products in the prehospital resuscitation phase.[17] A second RCT in adults with severe traumatic injury showed the use of crystalloids in the prehospital phase of resuscitation decreased the risk of survival compared to not using any crystalloids or blood products.[18]

Pediatric and adult data supports the association of crystalloids with worse outcomes and the increased and early use of blood products (whole blood or balanced approach) with improved survival. These data support our recommendation suggesting the prioritization of blood products over crystalloids for the resuscitation of traumatic hemorrhagic shock in children.

1.2: In traumatically injured children in hemorrhagic shock, the use of low titer (≤ 200 Ig G) group O whole blood might be considered if available over individual blood components (RBC, plasma, and platelets) for resuscitation. *Clinical Recommendation, conditional recommendation, very low certainty of evidence, 94% agreement (n=16), Median 8.5, IQR: 7.75-9.*

Rationale**:** When compared to individual blood components in a balanced ratio, low titer group O whole blood (LTOWB) is more potent due to less anticoagulants, less preservatives increasing hemoglobin, platelet concentrations, and coagulation factors.[19] In addition, storage of platelets at 4°C may also make LTOWB more hemostatic. In addition, whole blood causes less dilutional coagulopathy and less hypocalcemia due to the increased citrate when transfusing multiple blood components.[20] Due to the exclusive use of a group O product, whole blood may be safer than use of components by preventing transfusion of incompatible ABO unit(s) that may lead to a fatal hemolytic reaction due to human error.[21] In addition, the storage of whole blood at 4°C reduces the risk of bacterial contamination that exists with the use of platelets stored at room temperature.[22] Finally, whole blood has logistic advantages due to the need to only dispense one product from the blood bank and administer one product at the bedside instead of dispensing and administering individual blood components.

Using LTOWB instead of individual blood components in children more rapidly provides RBCs, plasma and platelets to children with severe traumatic bleeding, more effectively resolves shock and coagulopathy,[23] is associated with less total amount of blood products administered and mechanical ventilation days,[24] and is independently associated with increased 72 hour (OR 0.23; [0.08-0.70]), and 28 day mortality (OR 0.41; [0.23-0.98]) in a single center retrospective study.[8]

Adult data indicates the use of LTOWB compared to individual blood components is independently associated with improved 24 hour and 28 day survival and is also associated with less (40-60%) total blood products administered.[25-27] Data from studies performed on children and adults suggest no increased risk of hemolysis in non-group O recipients and no increase in any other adverse outcomes to include organ failure.[28-30]

1.3: In traumatically injured children in hemorrhagic shock, when utilizing blood component resuscitation, we suggest targeting high plasma:RBC ratios (1:1) to minimize the plasma deficit. *Consensus Panel Expertise, 100% agreement (n=16), median 9, IQR: 8-9.*

Rationale**:** Children with life threatening hemorrhage from traumatic injuries develop shock due to hypoperfusion. This hypoperfusion causes endothelial injury with loss of the glycocalyx and increased endothelial permeability. The endothelial injury leads to inflammation which can further exacerbate endothelial injury and lead to the production of increased activated protein C and tissue plasminogen activator directly causing trauma induced coagulopathy. While this pathophysiology has been mainly described in adults, there is data indicating it may also occur in children.[31-33] Differences in hemostasis mechanisms between children and adults will require additional study to establish whether these mechanisms are also observed in children.[34] To address the shock, endothelial, immune and hemostatic dysfunction, a balanced resuscitation with plasma and RBCs may be optimal because plasma may repair the endothelium and mitigate capillary leak and improve intravascular volume. Plasma may also improve hemostasis by providing coagulation factors for patients who have developed a consumptive coagulopathy. These potential effects of plasma may improve intravascular volume, reduce extravascular edema and bleeding which can all lead to improved oxygen delivery.

A two-year retrospective review of the pediatric trauma quality improvement program (TQIP) supports that the increased plasma:RBC ratios minimize plasma deficit. In this study of over 500 massively transfused children, the plasma:RBC ratio, as a continuous variable, was associated with improved 24-hour mortality (OR 0.47; [0.28-0.80]). In this same study, a plasma:RBC ratio > 1:1 was also independently associated with reduced 24-hour mortality (OR 0.48; [0.26-0.88]). In a multi-institutional prospective observational study that included 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; [0.13-0.99]). When the plasma deficit (RBC ml/kg – plasma ml/kg) was analyzed, an increased deficit was also associated with increased 24 hour mortality (OR 1.2; [1.05-1.3]).[4] Additional publications that do not report an association of increased plasma:RBC ratios with improved outcomes have significant limitations to include the lack of adjusted analyses and small sample size or single center studies.[27, 35, 36] Adult data supporting the use of high ratios targeting 1:1 include the PROPPR trial that reported reduced death from bleeding at 24 hours and improved time to cessation of bleeding.[37] The PAMPer trial also reported improved survival when plasma was used early in the prehospital phase of resuscitation.[38]

1.4: In traumatically injured children in hemorrhagic shock, when utilizing blood component resuscitation, targeting a high platelet to RBC weight-based ratio of 1:1 to minimize the platelet deficit is suggested. *Consensus Panel Expertise, 100% agreement (n=16), median 8, IQR: 7-9.*

Rationale**:** Platelet dysfunction occurs early in traumatic blood failure in adults and the transfusion of platelets may reverse it.[37] The importance of the platelets within hemostasis is another reason to hypothesize that the use of platelets may reduce bleeding and improve outcomes. In addition, in vitro and animal evidence suggest that platelet transfusion may repair the injured endothelium, which could also improve outcomes.[39, 40]

Data supporting the early use of platelets in children was also published in the aforementioned multi-institutional prospective observational study in children with life threatening bleeding. In this study, a platelet deficit (RBC ml/kg – platelet ml/kg) was independently associated with increased mortality at 24 hours (OR 1.1 [1.05-1.2]) but there was no survival advantage associated with the platelet: RBC ratio.[4] A plausible explanation for this may be that the deficit more accurately reflects the lack of balance between platelets and RBCs more than a ratio which does not incorporate the magnitude of the imbalance. Additional adult data supporting the early use of platelets, a secondary analysis of PROPPR trial focusing on platelet transfusions, demonstrated improved survival in these patients who achieved a more balanced resuscitation.[41]

2) Pre-hospital blood products use in pediatric traumatic hemorrhagic shock

2.1: In traumatically injured children in hemorrhagic shock, it is reasonable to consider prehospital transfusion by out-of-hospital EMS for injured children based on product availability and clinical judgement. *Consensus Panel Expertise, 100% agreement (n=16), median 8, IQR: 8-8.25.*

Definition for purpose of this recommendation: Out-of-hospital EMS is defined as all medical care for a trauma patient that occurs in a non-health care setting, including scene response and interhospital transfer.

***Rationale*:** Death due to bleeding most often occurs early after injury.[42] Delays in time to transfusion are associated with increased mortality and increased time to hemostasis.[43] The rationale for prehospital transfusion is to shift resuscitation earlier to address blood loss, mitigate shock and coagulopathy, and ultimately reduce mortality and morbidity for injured patients.

Little high-quality evidence has defined the optimal approach to fluid resuscitation and transfusion by out-of-hospital EMS in children with hemorrhagic shock. The management of acute life-threatening bleeding has been studied almost exclusively in adult trauma, where early blood product use by out-of-hospital EMS providers has become an accepted and common practice. In military[44-46] and civilian[38, 47] adult cohorts, the use of blood products as the first resuscitative fluid has been associated with improved survival. No studies to date have reported survival benefits of prehospital blood product transfusion in children.

The transfusion of blood products by out-of-hospital EMS providers is feasible and safe.[48, 49] Data show that the LTOWB[49], red blood cells and plasma[48] under pediatric dosing protocols is feasible, acceptable to providers, and not associated with adverse transfusion-related events.[50] Only two studies have compared outcomes between matched pediatric cohorts who received blood products prehospital versus in-hospital. These studies are limited by sample size and moderate bias due to outcome measurement and confounding.[50, 51] Though the studies were not adequately powered to detect a difference in mortality; authors did report that the prehospital transfusion groups did receive less in-flight crystalloid, had higher admission fibrinogen levels, and faster time to normalization of the international normalized ratio (INR).[51] This recommendation has to take into account the ability of blood products and comfort level of the practice of regional Emergency Medical Services. However, the above literature suggests that there is evidence that this can be organized and safely utilized in pediatric trauma patients with hemorrhagic shock.

3) Use of tranexamic acid and other hemostatic adjuncts in pediatric traumatic hemorrhagic shock

3.1: In traumatically injured children with hemorrhagic shock, the empiric use of tranexamic acid within 3 hours of injury might be considered. *Clinical Recommendation, conditional recommendation, very low certainty of evidence, 80% agreement (n=15), median 7, IQR: 7-8.*

***Rationale*:** Fibrinolytic dysregulation is an important mechanism in traumatic coagulopathy that consists of a spectrum ranging from excessive breakdown (hyperfibrinolysis), physiologic fibrinolysis, and fibrinolytic shutdown. Injury to the vascular bed with endothelial disruption initiates a complex interaction between the endothelium, platelets, and coagulation factors ultimately resulting in thrombin generation and cross-linking of fibrin monomers. This interaction results in the formation of a mature clot, seals the area of vascular injury, and leads to hemostasis. Fibrinolysis is a physiologic process occurring in parallel with fibrin cross-linking to prevent the extension of this process beyond the injury. During injury, this process can turn from physiologic to pathologic to increased or reduced fibrinolysis, which have both been associated with high mortality.[52] This increases the importance of timely identification and treatment of fibrinolytic dysregulation in trauma patients. Tranexamic acid (TXA), an antifibrinolytic agent, has been extensively studied in adult trauma trials in an effort to improve outcomes in patients with hyperfibrinolysis.[53-55] We did not identify any randomized clinical trials evaluating TXA in severely injured children. There were five observational studies (four retrospective and one prospective study) that compared empiric TXA use versus no TXA, controlling for confounders. Three of the studies were in civilian settings and two in combat settings. One combat associated paper evaluated a registry of 766 children of 9% received TXA.[7] Using propensity score match analysis, they found that TXA was independently associated with a lower odds of mortality (OR 0.87; [0.85-0.89]). The second combat study, also evaluated a registry of children receiving massive transfusion, demonstrated that TXA use was associated with a lower odds of mortality (OR 0.35; [0.12-0.99]).[56] A prospective observational study of children with life-threatening bleeding showed that antifibrinolytic agents (TXA or aminocaproic acid) were associated with decreased 6 and 24 hour mortality (6 hour: adjusted OR 0.29; [0.09-0.93]; 24 hour: aOR 0.45; [0.21-0.98]) compared to those that received no antifibrinolytic agent [57] Two retrospective studies did not find an association between TXA use and improved outcomes. One study evaluated a large administrative trauma database in Japan with a propensity matched analysis of children who did and did not receive TXA.[58] They found no difference in mortality between groups. However, based on a low mean ISS of 10, they may not have identified pediatric population most at risk for hemorrhagic shock. The second retrospective study evaluated massively transfused injured children and compared patients who received TXA to those who did not.[59] They found no mortality difference between groups, but this study had a small sample size (n=48).

There is strong evidence for empiric TXA in severely injured adults. The CRASH-2 randomized control trial randomized over 20,000 injured adults.[60] Compared to placebo, TXA decreased death from bleeding by one-third if given within 3 hours from injury. Several additional prospective adult randomized studies also have found a strong correlation of TXA administration with survival if given soon after injury, including when given to head injured patients.[61-63]

3.2: In traumatically injured children with hemorrhagic shock, we recommend the use of tranexamic acid over aminocaproic acid when an antifibrinolytic agent is being considered. *Consensus Panel Expertise, 93% agreement (n=15), median 8, IQR: 7-9.*

Rationale**:** No high-quality studies comparing TXA to aminocaproic acid have been published in a pediatric trauma population. However, a much broader body of adult and pediatric trauma and surgical literature exist to show the efficacy and safety of TXA than for aminocaproic acid.[7, 53, 55, 56, 64-66] In addition, some data suggest an association between acute kidney injury and aminocaproic acid use in all children with life threatening bleeding.[57]

3.3: In traumatically injured children with hemorrhagic shock, there is insufficient evidence for the empiric use of prothrombin concentrate. *Consensus Panel Expertise, 93% agreement (n=15), median 9, IQR: 7-9.*

Rationale**:** Prothrombin complex concentrate (PCC), contains either three or four of the vitamin K-dependent coagulation factors (II, IX, X, and sometimes VII), and may be an alternative approach, to FFP, for correction of coagulopathy.[67] Although the literature is limited, adult literature in both trauma and operative settings support the administration of PCC to bleeding patients to reverse coagulopathy.[68, 69] No high-quality studies evaluating the use PCC in a pediatric trauma population were identified. In a small retrospective study of a mixed pediatric population with only half experiencing trauma, PCC was found to improve INR but had no effect on outcomes.[70] While PCC is commonly used as a reversal agent in bleeding associated with vitamin K antagonists or direct oral anticoagulants, there is little clinical or physiologic evidence that PCC has any benefit as an empiric treatment for traumatically injured children in hemorrhagic shock.

3.4: In traumatically injured children with hemorrhagic shock, there is insufficient evidence that the use of viscoelastic monitoring to guide antifibrinolytic therapy improves patient outcomes. *Consensus Panel Expertise, 94% agreement (n=16), median 7, IQR: 7-8.25.*

Rationale**:** Several studies have identified that children with hyperfibrinolysis have a higher mortality after injury.[71, 72] Given this observation and the understanding of the antifibrinolytic effects of TXA, researchers would suggest that those children with hyperfibrinolysis should be identified and targeted for TXA.[73] Some pediatric trauma centers may utilize VEM to evaluate trauma patients for coagulopathy and fibrinolysis in addition to conventional coagulation testing. However, the selective use of TXA based on VEM has not been studied in children and the limited adult studies for rapid-thromboelastography (r-TEG) guided TXA administration have failed to show a clear benefit.[74] Until additional literature evaluates the specific utilization of VEM prior to and following administration of TXA in pediatric patients with different postinjury fibrinolysis subtypes, we cannot recommend use of VEM in this setting.

3.5: In traumatically injured children with hemorrhagic shock, there is insufficient evidence for the empiric use of fibrinogen supplementation (cryoprecipitate or fibrinogen concentrates). *Consensus Panel Expertise, 87% agreement (n=15), median 7, IQR: 7-8.*

Rationale**:** No studies were identified supporting the empiric use of fibrinogen or cryoprecipitate in pediatric hemorrhagic trauma. There have been several adult studies investigating the use of fibrinogen supplementation, however a meta-analysis of these studies failed to show a mortality benefit.[75]

3.6: In traumatically injured children with hemorrhagic shock, we suggest the replacement of fibrinogen in the setting of hypofibrinogenemia. *Consensus Panel Expertise, 87% agreement (n=16), median 8, IQR: 8-9.*

***Rationale*:** It is established that fibrinogen is an essential substrate for clot formation, and that low fibrinogen can lead to severe bleeding whether congenital or acquired.[31] In the setting of trauma, low fibrinogen is essentially due to consumption. Most trauma centers will screen patients for hypofibrinogenemia, particularly during a massive transfusion, and correct if the fibrinogen level is below 150 mg/dL.[76] Low fibrinogen levels can be corrected either by the administration of fibrinogen concentrate or cryoprecipitate. VEM has been used to identify low fibrinogen, based on prolonged R time, low alpha angle, or low maximum amplitude. Rotational thromboelastometry can also be utilized. A pediatric study is underway studying early fibrinogen concentrate in pediatric patients presenting with a FIBTEM (extrinsically activated thromboelastometric test with cytochalasin D) A5 of <=10.[77] This study may provide us additional guidance for using of fibrinogen in pediatric trauma patients.

4) Use of tourniquets in pediatric traumatic hemorrhagic shock

4.1: In traumatically injured children with exsanguinating extremity hemorrhage, we recommend the use of commercially available tourniquets by individuals with training. *Consensus Panel Expertise, 88% agreement (n=16), median 9, IQR: 7.75-9.*

***Rationale*:** In the past, the use of tourniquets for exsanguinating extremity hemorrhage has had mixed impact on outcomes, mainly related to inappropriate applications by untrained responders. In earlier military conflicts, challenges with delays in reaching definitive care led to complications including the risk of limb loss.[78, 79] Recent adult military experience with quicker transport times and enhanced training among soldiers/first responders showed a clear survival advantage among those with tourniquet use.[80] These data along with a dramatic increase in mass casualty events have influenced a paradigm shift among first responders in civilian settings toward tourniquet use.[81-84] Education of first responders has been advanced by a committed effort by the American College of Surgeons "Stop the Bleed' program. Concerns remain regarding the applicability of combat adult practice with relation to children in civilian settings. In these elective settings, tourniquet complications were found to occur in 0.4% to 1.4% of patients, with most injuries involving soft tissue or nerve damage.[85]

Our review of available evidence for the use of tourniquets in exsanguinating extremity hemorrhage in children yielded six manuscripts: four from a military setting[86-89] and two evaluating a civilian experience.[90, 91] These studies showed decreased crystalloid administration, decreased transfusion requirements and a survival advantage for children treated with tourniquets, particularly when applied before the onset of shock. There were no significant complications from tourniquet use. In the studies evaluated, challenges still exist with tourniquet use including tourniquet overuse, improper tourniquet application and a need for more standardized training.[90]

5)Pre-hospital intubation and blood pressure management in pediatric traumatic hemorrhagic shock

5.1: In traumatically injured children with hemorrhagic shock, we suggest against a permissive hypotension strategy and suggest resuscitation goals that optimize end organ perfusion and adequate oxygen delivery. *Consensus Panel Expertise, 93% agreement (n=15), median 7, IQR: 7-8.5.*

Rationale: Although some reports in the adult trauma literature suggest a potential benefit of permissive hypotension [92, 93], this has become more controversial.[94, 95] In pediatric trauma patients, there was insufficient evidence to evaluate this strategy. However, there is a widely accepted paradigm that children a significant ability to compensate until very late stages of hemorrhagic shock.[96] In Advanced Trauma Life Support (ATLS), the American College of Surgeons Committee on Trauma reports that a child has a low but normal blood pressure starting after 30% blood volume loss and experiences hypotension only after 45% blood volume loss.[97] Furthermore, a rigorous definition of permissive hypotension in pediatric patients could not be identified in the literature. Finally, in addition, injured children with hypotension may have a concomitant head injury for which permissive hypotension would not be a recommended strategy.

6) Resuscitation and use of hemostatic monitoring for pediatric traumatic hemorrhagic shock

6.1: In traumatically injured children with hemorrhagic shock, we suggest an initial empiric resuscitation approach utilizing massive transfusion protocols and balanced blood product administration. *Consensus Panel Expertise, 94% agreement (n=16), median 9, IQR: 7-9.*

Rationale: In severely injured adult trauma patients, empiric hemostatic resuscitation using balanced blood products or whole blood as part of a massive transfusion protocol (MTP) is standard of care.[98, 99] Although there have been many studies evaluating massively transfused children, a paucity of studies have critically examined the benefits of MTP implementation and use in children.[100] Three single center, retrospective studies specifically evaluated the impact of massive transfusion protocols on outcomes. A 2011 study compared 33 pre-MTP to 22 post-MTP children from a three-year period. The pre- and post-MTP groups included 31 and 16 trauma patients, respectively. Overall, there was no difference in mortality amongst the group even though the post-MTP implementation patients were more severely injured as assessed by injury severity score (ISS). The post-MTP group received more blood products and experienced less thromboembolic complications.[101] A second 2011 study compared 53 MTP patients to 49 non-MTP patients over a two-year period. There were no differences in baseline characteristics including ISS. The MTP group received plasma earlier and received a more balanced resuscitation, but no difference in mortality was observed.[102] Finally, a 2016 study compared 125 pre-MTP to 115 post-MTP implementation patients over a ten-year period. Despite the post-MTP cohort being more severely injured, there was no difference in mortality. Post-MTP patients received plasma and platelet transfusions earlier and in a more balanced ratio with red blood cells.[103] These studies suggest that massive transfusion protocols are safe and may provide benefit in the resuscitation of severely injured pediatric trauma patients in hemorrhagic shock.

6.2: In traumatically injured children with hemorrhagic shock, following empiric initial resuscitation, a goal directed resuscitation strategy to optimize hemostasis and correct coagulopathy is suggested. *Consensus Panel Expertise, 100% agreement (n=15), median 8, IQR: 7.5-9.*

***Rationale**:* A goal directed hemostatic resuscitation strategy to optimize hemostasis and correct coagulopathy is overwhelmingly recommended and supported by high quality evidence in traumatically injured adult patients.[98, 99] We were unable to identify a pediatric-focused study that directly compared a goal directed approach to a non-goal directed approach following initial resuscitation with a MTP. However, eight studies were identified describing the use of measures of hemostasis in the resuscitation of injured children. These studies illustrate the importance of assessing abnormalities in coagulation during the trauma resuscitation and early hospital course. Additionally, the identification and management of acute traumatic coagulopathy in pediatric trauma centers is further detailed in the American College of Surgeons Committee on Trauma's most recent iteration of the Resources for Optimal Care of the Injured Patient.[104] During the resuscitation process, tachycardia, hypotension, and clinical and laboratory markers of impaired end organ perfusion begin to resolve when hemodynamic stability is established. Continued administration of blood products as part of a massive transfusion protocol for hemodynamic resuscitation may be inefficient, costly, and potentially harmful. A transition to a more targeted approach for blood product administration to correct specific coagulation parameters is reasonable.

6.3: In traumatically injured children with hemorrhagic shock, adjunctive viscoelastic monitoring when available is suggested. *Consensus Panel Expertise, 100% agreement (n=15), median 8, IQR: 7-9.*

Rationale: In children, studies have shown that abnormalities in VEM parameters correlate with conventional coagulation tests (CCT) abnormalities, injury severity, and mortality.[105, 106] Studies in children have shown that compared to CCT, VEM parameters were more closely correlated with needing a life-saving intervention and mortality.[105, 106] A retrospective, multicenter study compared outcomes in children before and after implementing a VEM-based resuscitation strategy. Using propensity score matching, the authors found that patients that received a VEM-based resuscitation strategy had more timely results, received less 24-hour red blood cell and plasma volumes, were less coagulopathic after 24 hours, and had less total hospital days. There was no difference in mortality.[107]

Viscoelastic monitoring (VEM), including both thromboelastography (TEG) and rotational thrombelastometry (ROTEM), provide accurate and comprehensive depictions of traumatically injured adults coagulation profiles in hemorrhagic shock.[108] VEM provides more timely results compared to CCT.[109, 110] Randomized prospective studies in severely injured adults receiving an MTP-based resuscitation for hemorrhagic shock showed reduced morbidity and mortality in patients that received a VEM-based resuscitation.[110] We believe that utilization of VEM may aid in resuscitation of children in hemorrhagic shock, but as noted in recommendation 3.4, we do not believe there is sufficient data in children to utilize VEM for monitoring fibrinolysis or directing administration of TXA.

Conclusion

The Pediatric Traumatic Hemorrhagic Shock Consensus Conference aimed to provide guidance and recommendations for the resuscitation of traumatically injured children in hemorrhagic shock. Despite the lack of or low quality of the literature in the pediatric population, our expert panel has reached agreement on clinical recommendations, consensus and good practice statements to guide clinicians in care for these patients.

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Supplemental Digital Content

PTHSCC Supplement to the Methods

Supplemental Table 1. Hierarcy of Language utilized in Statements and Recommendations

Supplemental Table 2. Pediatric Traumatic Hemorrhagic Shock Consensus Conference (PTHSCC): Search Strategies for Systematic Reviews

Supplemental Figure 1. PRISMA Diagrams for Systematic Reviews

Supplemental Table 3. Articles Included for Blood Products and Fluid Resuscitation for Hemostatic Resuscitation

Supplemental Table 4. Articles Included for Utilization of Pre-hospital Blood Products

Supplemental Table 5. Articles Included for Use of Hemostatic Adjuncts

Supplemental Table 6. Articles Included for Tourniquet Use

Supplemental Table 7. Articles Included for Pre-hospital Airway and Blood Pressure Management

Supplemental Table 8. Articles Included for Conventional Coagulation Tests or Thromboelastography-guided Resuscitation

Appendix B: Good Practice Statements

Appendix B: Good Practice Statements

1) Blood products and fluid resuscitation in pediatric traumatic hemorrhagic shock

Good Practice Statement: In traumatically injured children in hemorrhagic shock, clinicians should account for volumes of blood products given from the time of injury prior to arrival at their facility when calculating plasma and platelet deficits. *Good Practice Statement, 100% agreement (n=16), median 9, IQR: 8.75-9.*

Rationale**:** In order to appropriately structure the ensuing resuscitation at the definitive care facility, it is advantageous to account for the volumes of products that have already been given. This will facilitate achieving a balanced resuscitation, which may improve outcomes for children with life threatening hemorrhage from traumatic injury.

2) Pre-hospital blood products use in pediatric traumatic hemorrhagic shock

No good practice statements were generated for this subtopic.

3) Use of tranexamic acid and other hemostatic adjuncts in pediatric traumatic hemorrhagic shock

Good Practice Statement: In traumatically injured children with hemorrhagic shock, calcium should be replaced if hypocalcemia is suspected or confirmed. *Good Practice Statement, 94% agreement (n=16), median 9, IQR: 7.75-9.*

Rationale: Calcium is an essential element for coagulation, a critical cofactor for many of the proteins in coagulation cascade, an important factor in stabilizing and cross-linking fibrin, and important in platelet activation and function.[1] Blood products that contain citrate can chelate calcium, especially plasma and platelets. The chelation of calcium, if not recognized, can lead to hypocalcemia and potentially increased bleeding. Patients presenting with traumatic shock and hypocalcemia have increased transfusion requirements.[2] Given this background, strong consideration should be given toinclude calcium as part of initial goal-directed resuscitation in the setting of hemorrhagic shock.[1]

4) Use of tourniquets in pediatric traumatic hemorrhagic shock

Good Practice Statement: In traumatically injured children with exsanguinating extremity hemorrhage, we recommend the use of commercially available tourniquets by individuals with training. *Good Practice Statement, 88% agreement (n=16), median 9, IQR: 7.75-9.*

Rationale**:** In the past, the use of tourniquets for exsanguinating extremity hemorrhage has had mixed impact on outcomes, mainly related to inappropriate applications by untrained responders. In earlier military conflicts, challenges with delays in reaching definitive care led to complications including the risk of limb loss.[3, 4] Recent adult military experience with quicker transport times and enhanced training among soldiers/first responders showed a clear survival advantage among those with tourniquet use.[5] These data along with a dramatic increase in mass casualty events have influenced a paradigm shift among first responders in civilian settings toward tourniquet use.[6-9] Education of first responders has been advanced by a committed effort by the American College of Surgeons "Stop the Bleed' program. Concerns remain regarding the applicability of combat adult practice with relation to children in civilian settings.

In these elective settings, tourniquet complications were found to occur in 0.4% to 1.4% of patients, with most injuries involving soft tissue or nerve damage.[10]

Our review of available evidence for the use of tourniquets in exsanguinating extremity hemorrhage in children yielded six manuscripts: four from a military setting[11-14] and two evaluating a civilian experience.[15, 16] These studies showed decreased crystalloid administration, decreased transfusion requirements and a survival advantage for children treated with tourniquets, particularly when applied before the onset of shock. There were no significant complications from tourniquet use. In the studies evaluated, challenges still exist with tourniquet use including tourniquet overuse, improper tourniquet application and a need for more standardized training.[15]

Good Practice Statement: In traumatically injured children with exsanguinating extremity hemorrhage, when tourniquets are applied, providers should document the time of application and minimize the total time of application as clinically feasible. *Good Practice Statement, 100% agreement (n=16), median 8, IQR: 8-9.*

Rationale: Physiologic responses of children to tourniquets in controlled operating room settings have demonstrated changes including an increase in metabolic acidosis, hypercarbia, and temperature related to tourniquet use.[17-21] Tourniquet times greater than 75 minutes demonstrate lactic acidosis that correlates linearly with increasing tourniquet time.[22] Additionally, complications related to tourniquet application are directly related to technique and duration.

5)Pre-hospital intubation and blood pressure management in pediatric traumatic hemorrhagic shock

Good Practice Statement: In traumatically injured children with hemorrhagic shock, if tracheal intubation and positive pressure ventilation are deemed necessary, prior or parallel resuscitation, preferably with blood products if available, is necessary to mitigate post intervention reduction of cardiac output and risk for cardiac arrest. *Good Practice Statement, 93% agreement (n=15), median 7, IQR: 7-8.5.*

***Rationale*:** Insufficient evidence was identified to base a specific consensus recommendation concerning absolute priorities in a resuscitation for pediatric hemorrhagic shock. This statement reflects the consensus panels' recognition of the physiologic consequences of tracheal intubation (including medications to facilitate intubation) and positive pressure ventilation in the setting of hemorrhagic shock and hypovolemia.

Good Practice Statement: In traumatically injured children with hemorrhagic shock, when arterial hemorrhage is known or suspected, special attention should be paid to clinically significant hypertension which could worsen bleeding. *Good Practice Statement, 80% agreement (n=15), median 7, IQR: 7-7.*

***Rationale*:** This statement reflects the consensus panels' general recognition that clinically significant hypertension may exacerbate arterial hemorrhage. Recognizing that in traumatically injured pediatric patients, hypertension in the setting of coexistent head trauma may reflect an important homeostatic compensatory response to increased intracranial pressure.

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Pediatri

c Traumatic Hemorrhagic Shock Consensus Conference Recommendations

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Data Supplement

Table of Contents

PTHSCC Methods

The methodology for the Pediatric Traumatic Hemorrhagic Shock Consensus Conference (PTHSCC) was modeled after the Pediatric Critical Care Transfusion and Anemia Expertise Initiative (TAXI)[1] and followed the standards set by the Institute of Medicine for guideline development to create comprehensive evidence-based and when evidence was lacking, expert based recommendations for decision making in pediatric trauma patients experiencing hemorrhagic shock.

Expert Panel

Experts were selected to represent the medical fields that participate in the care of a critically ill pediatric trauma patient: pediatric anesthesiology, emergency medicine, critical care medicine, transfusion medicine/hematology and surgery based on the last 5 years of publications on topics covered within the consensus conference and leadership in professional societies and research networks related to the topic of interest.

The PTHSCC process included systematic reviews and one consensus meeting, with substantial work prior to the meeting for subtopic selection, development of Population, Intervention, Comparison, Outcome, Timing (PICOT) questions, literature search and evaluation of its results, and risk of bias assessment. Systematic reviews were conducted by a team at University of Alabama Birmingham that included medical librarians and research assistants (see **Acknowledgments**), using a limited interaction model with the guideline development group.[2] Sixteen content experts and 1 non-voting implementation expert representing 12 academic institutions and 6 medical specialties agreed and participated in all aspects of PTHSCC. International experts were initially invited and agreed to participate, however their participation was precluded by travel restrictions related to the COVID-19 pandemic. Potential conflicts of interest were reviewed at the time of agreement to participation and again at the time of publication.

Subtopics

Experts were organized in 6 subgroups that each focused on a clinical subtopic for pediatric trauma patients experiencing hemorrhagic shock: 1) blood products and fluid resuscitation for hemostatic resuscitation, 2) utilization of pre-hospital blood products, 3) use of hemostatic adjuncts, 4) tourniquet use, 5) pre-hospital airway and blood pressure management, and 6) conventional coagulation tests or thromboelastography-guided resuscitation.

The experts agreed upon a common definition with strong agreement by anonymous voting via Qualtrics (Provo, UT), using the Research and Development/UCLA Appropriateness scale ranging from 1 (strongly disagree) to 9 (strongly agree).[3] "Hemorrhagic shock" was defined as form of hypovolemic shock, that is potentially life threatening, characterized by severe blood loss (internal and/or external) leading to inadequate oxygen delivery at the cellular level that may manifest in physiologic responses of hypotension and tachycardia, and a number of laboratory abnormalities measuring cellular hypoperfusion to include base deficit, elevated lactate values, and decreased hemoglobin.[4] (Consensus Panel Voting, 100% agreement (n=16), median 8.75, IQR 8.75-9).

Systematic reviews and data synthesis

We performed comprehensive searches in the following databases: Ovid MEDLINE (1946-January 2022, Ovid EMBASE (1974-January 2022), CinicalTrials.gov, and Cochrane Library (Wiley), for the 6 subtopics. Electronic searches and study retrieval were conducted with the assistance of the Lister Hill Library at the University of Alabama. A combination of relevant subject headings and key words were used to identify the specific subpopulations desired. No language, publication date, or article-type restrictions were applied to the searches except where noted in **Supplemental Table 1**. Database search results were deduplicated and screened using the Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia). Several studies were identified through hand-search and these were included in the original number of studies to be screened and underwent the title/abstract screening in the same pool as the electronic search citations.

Studies were eligible for inclusion if the study population consisted of children (≤18 years) sustaining trauma and mixed adult and pediatric trauma populations (if the pediatric subpopulation could be separated) at risk for or with hemorrhagic shock. Studies were excluded if they were 1) not related to the subtopic of interest; 2) adult-only study population; 3) animal-only studies; 5) not original data (i.e. reviews, editorials, commentaries, and meeting proceedings); 6) case reports or series with sample size ≤ to 10 patients; 7) abstract only; or 8) not in English language.

Two independent reviewers (R.T.R, J.P.E, A.B., P.A) screened abstracts and then full text articles meeting inclusion/exclusion criteria. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagrams for each topic are included in the Online Supplement. (**Supplemental Figure 1**) Included full text articles were then shared with each subgroup for review and development of: graded clinical recommendations, ungraded good practice statements[5] and ungraded expert consensus statements. The heterogeneity of the studies and outcomes allowed the Grading of Recommendations, Assessement, Development, and Evaluation (GRADE) methodology to be utilized for grading the strength of the recommendations for only two clinical recommendations. We used GRADEpro Guideline Development Tool online software (McMaster University, Hamilton, Ontario, Canada) to develop evidence profiles for each PICOT question.[6, 7] Good practice statements[5, 8] and expert consensus statements were developed when the quality of the evidence was poor or lacking and could not be graded. The hierarchy of language utilized in the statements and recommendations is described in **Supplemental Table 1**.

Risk of Bias was assessed using the Quality in Prognostic Studies (QUIPS) tool.[9] A low risk of bias was assigned if all six domains were scored as low, or if not more than two moderate or unknown risks of bias were identified. Moderate risk of bias was assigned when three or less risk of bias domains were scored moderate, or unknown, in combination with no high risk of bias. Moderate was also assigned when one domain was scored as a high risk of bias in combination with one or less moderate or unknown risks of bias. A high risk of bias was assigned when two or more domains scored a high risk of bias, or four or more moderate or unknown risk of bias.[10]

Recommendations that has low or very low quality evidence or no pediatric evidence were presented with justification and rationale by each subtopic group leader for full group expert consensus. Using the Research and Development/University of California, Los Angeles (RAND/UCLA) appropriateness method,[3] consensus panel voting, to reach consensus agreement or disagreement with a specific statement, was performed utilizing Qualtrics (Provo, UT). Agreement was defined a priori as 80% of the experts rating the recommendation a 7, 8, or 9. Recommendations that did not achieve initial agreement were revised and discussed by the consensus committee with subsequent voting until agreement was obtained. Among 21 statements and clinical recommendations, 7 statements reached agreement during the first round of voting. The remaining 14 statements moved to the second round of voting, with 10 reaching agreement. Lastly, 4 statements were reformulated and reached agreement during the third round of voting.

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Supplemental Table 1. Hierarcy of Language utilized in Statements and Recommendations

Certainty →	CARRY OUT OR DO	DO NOT DO	Certainty →
	Is recommended		
	Should be selected / used		
	We suggest		
	Is suggested		
	Might be considered	May not be beneficial	
	Uncertain whether there is any benefit	Unlikely to benefit	
	Insufficient evidence	Insufficient evidence	

Supplemental Table 2. Pediatric Traumatic Hemorrhagic Shock Consensus Conference (PTHSCC): Search Strategies for Systematic Reviews

Blood Products and Fluids for Hemostatic Resuscitation	
Database: PubMed July 27, 2020 Searcher: Geeta Malik Intervention: Whole Blood compared to Component Therapy Results: 129 Upated January 2022: Results: 65	("shock, hemorrhagic"[MeSH Terms] OR "hemorrhagic-shock"[Text Word]) AND ((("Wounds and Injuries"[MeSH Terms] OR "injuries"[MeSH Subheading]) OR "Accidents"[MeSH Terms]) OR ("trauma*"[Text Word] OR "injur*"[Text Word])) **AND** Whole-blood OR "Blood"[Mesh:NoExp] **AND** Blood-Product*[tiab] OR "Blood Component Transfusion"[Mesh] OR Blood-transfusion-component*[tiab] OR Erythrocyte-transfusion*[tiab] OR Leukocyte-transfusion*[tiab] OR Lymphocyte-transfusion*[tiab] OR Platelet-transfusion*[tiab] OR Hemostatic-resuscitation[tiab] OR Blood-cells[tiab] OR Blood-platelet* OR Blood-plasma OR Blood serum)
Database: Embase Date: 8/5/20 Searcher: Kay Smith & Jill Deaver Intervention: Whole Blood compared to Component Therapy Filters: Non-medline; articles and reviews only (no conference abstracts) Results: 2	('hemorrhagic shock'/exp OR 'hemorrhagic shock' OR ((h?emorrhagic NEAR/3 shock):ti,ab,kw) OR ((bleeding NEAR/3 shock):ti,ab,kw)) AND ('injury'/exp OR 'injury' OR trauma*:ti,ab,kw OR injur*:ti,ab,kw) AND ('blood'/exp/mj OR 'whole blood':ti,ab,kw OR 'human blood':ti,ab,kw) AND ('blood product':ti,ab,kw OR 'blood component therapy'/exp/mj OR 'blood component transfusion':ti,ab,kw OR 'transfusion blood component':ti,ab,kw) AND [embase]/lim NOT ([embase]/lim AND [medline]/lim) AND ('article'/it OR 'review'/it)
Database: Clinical Trials.gov July 21, 2020 Searcher: Geeta Malik Intervention: Whole Blood compared to Component Therapy Results: 15 Upated January 2022: Results: 6	Trauma OR injury[Other terms] Hemorrhagic Shock [Condition or disease] Whole Blood OR blood-component-therapy OR blood-transfusion-component [Intervention/treatment]
Database: Cochrane Library Date: 8/3/20 Searcher: Kay Smith Intervention: Whole Blood compared to Component Therapy Results: 7 trials (1 duplicated removed in EndNote from 8 trials results total)	#1 MeSH descriptor: [Shock, Hemorrhagic] explode all trees98 #2 (hemorrhagic shock):ti,ab,kw (Word variations have been searched) 804 #3 #1 OR #2 804 #4 MeSH descriptor: [Wounds and Injuries] explode all trees 24996

	#5 MeSH descriptor: [Accidents] explode all trees 5783 #6 MeSH descriptor: [] explode all trees and with qualifier(s): [injuries - IN] 3299 #7 (injuries):ti,ab,kw (Word variations have been searched) 56774 #8 (trauma):ti,ab,kw (Word variations have been searched) 14648 #9 #4 OR #5 OR #6 OR #7 OR #8 78799 #10 #3 AND #9 279 #11 MeSH descriptor: [Blood] this term only 526 #12 (whole blood):ti,ab,kw (Word variations have been searched) 11924 #13 #11 OR #12 12421 #14 MeSH descriptor: [Blood Component Transfusion] explode all trees 1048 #15 (blood transfusion component):ti,ab,kw (Word variations have been searched) 752 #16 (Erythrocyte transfusion):ti,ab,kw (Word variations have been searched) 2276 #17 (Leukocyte transfusion):ti,ab,kw (Word variations have been searched) 627 #18 (Lymphocyte transfusion):ti,ab,kw (Word variations have been searched) 359 #19 (Platelet transfusion):ti,ab,kw (Word variations have been searched) 3129 #20 (Hemostatic resuscitation):ti,ab,kw (Word variations have been searched) 61 #21 (blood cells):ti,ab,kw (Word variations have been searched) 48104 #22 (blood platelet):ti,ab,kw (Word variations have been searched) 14109 #23 (blood plasma):ti,ab,kw (Word variations have been searched) 68899 #24 (blood serum):ti,ab,kw (Word variations have been searched) 64718 #25 #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 159526 #26 #10 AND #13 AND #25 8
Database: PubMed Date: July 27, 2020 Searcher: Geeta Malik	("shock, hemorrhagic"[MeSH Terms] OR "hemorrhagic-shock"[Text Word]) AND ((("Wounds and Injuries"[MeSH Terms] OR "injuries"[MeSH Subheading]) OR "Accidents"[MeSH Terms]) OR

Intervention: Volume of Blood Products compared to Volume of Fluid resuscitation Results: 156 Upated January 2022: Results: 72	("trauma*"[Text Word] OR "injur*"[Text Word])) **AND** Volume AND (Blood-Product*[tiab] OR "Blood Component Transfusion"[Mesh] OR Blood-transfusion-component*[tiab] OR Erythrocyte-transfusion*[tiab] OR Leukocyte-transfusion*[tiab] OR Lymphocyte-transfusion*[tiab] OR Platelet-transfusion*[tiab] OR Hemostatic-resuscitation[tiab] OR Blood-cells[tiab] OR Blood-platelet* OR Blood-plasma OR Blood-serum) **AND** Volume AND (fluid-resuscitation OR "Fluid Therapy"[Mesh] OR fluid-therap*[tiab])
Database: Embase Date: 8/5/20 Searcher: Kay Smith & Jill Deaver Intervention: Volume of Blood Products compared to Volume of Fluid resuscitation Filters: Non-medline; articles and reviews only (no conference abstracts) Results: 4 (1 duplicate removed in EndNote from 5 total results)	('hemorrhagic shock'/exp OR 'hemorrhagic shock' OR ((h?emorrhagic NEAR/3 shock):ti,ab,kw) OR ((bleeding NEAR/3 shock):ti,ab,kw)) AND ('injury'/exp OR 'injury' OR trauma*:ti,ab,kw OR injur*:ti,ab,kw) AND ('blood volume'/exp/mj OR 'blood volume determination'/exp/mj OR (volume NEAR/3 blood NEAR/3 products) OR (volume:ti,ab,kw AND blood:ti,ab,kw AND products:ti,ab,kw)) AND ('fluid resuscitation'/exp OR ((fluid* NEAR/3 (therap* OR resuscitat*)):ti,ab,kw)) AND volume:ti,ab,kw AND [embase]/lim NOT ([embase]/lim AND [medline]/lim) AND ('article'/it OR 'review'/it)
Database: Clinical Trials.gov July 21, 2020 Searcher: Geeta Malik Intervention: Volume of Blood Products compared to Volume of Fluid resuscitation Results: 1	Trauma OR injury[Other terms] Hemorrhagic Shock [Condition or disease] Volume AND (blood-product OR fluid-resuscitation) [Intervention/treatment]
Database: Cochrane Library Date: 8/3/20 Searcher: Kay Smith Intervention: Volume of Blood Products compared to Volume of Fluid resuscitation Results: 2 reviews, 12 trials (7 duplicates removed in EndNote from 19 trials results total)	#1 MeSH descriptor: [Shock, Hemorrhagic] explode all trees98 #2 (hemorrhagic shock):ti,ab,kw (Word variations have been searched) 804 #3 #1 OR #2 804 #4 MeSH descriptor: [Wounds and Injuries] explode all trees 24996 #5 MeSH descriptor: [Accidents] explode all trees 5783 #6 MeSH descriptor: [] explode all trees and with qualifier(s): [injuries - IN] 3299 #7 (injuries):ti,ab,kw (Word variations have been searched) 56774 #8 (trauma):ti,ab,kw (Word variations have been searched) 14648

	#9 #4 OR #5 OR #6 OR #7 OR #8 78799 #10 #3 AND #9 279 #11 MeSH descriptor: [Blood Component Transfusion] explode all trees 1048 #12 (blood transfusion component):ti,ab,kw (Word variations have been searched) 752 #13 (Erythrocyte transfusion):ti,ab,kw (Word variations have been searched) 2276 #14 (Leukocyte transfusion):ti,ab,kw (Word variations have been searched) 627 #15 (Lymphocyte transfusion):ti,ab,kw (Word variations have been searched) 359 #16 (Platelet transfusion):ti,ab,kw (Word variations have been searched) 3129 #17 (Hemostatic resuscitation):ti,ab,kw (Word variations have been searched) 61 #18 (blood cells):ti,ab,kw (Word variations have been searched) 48104 #19 (blood platelet):ti,ab,kw (Word variations have been searched) 14109 #20 (blood plasma):ti,ab,kw (Word variations have been searched) 68899 #21 (blood serum):ti,ab,kw (Word variations have been searched) 64718 #22 #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 159526 #23 MeSH descriptor: [Fluid Therapy] explode all trees 1661 #24 (blood product):ti,ab,kw (Word variations have been searched) 27331 #25 #22 OR #24 170198 #26 (fluid resuscitation):ti,ab,kw (Word variations have been searched) 1493 #27 (fluid therapy):ti,ab,kw (Word variations have been searched) 13873 #28 #23 OR #26 OR #27 14423

	#29 (volume):ti,ab,kw (Word variations have been searched) 79511 #30 #25 AND #29 14134 #31 #28 AND #29 3353 #32 #10 AND #30 AND #31 21
Database: PubMed July 27, 2020 Searcher: Geeta Malik Intervention: High Plasma ratio resuscitation versus Low Plasma Ratio Resuscitation Results: 129 Upated January 2022: Results: 53	("shock, hemorrhagic"[MeSH Terms] OR "hemorrhagic-shock"[Text Word]) AND ((("Wounds and Injuries"[MeSH Terms] OR "injuries"[MeSH Subheading]) OR "Accidents"[MeSH Terms]) OR ("trauma*"[Text Word] OR "injur*"[Text Word])) **AND** (high OR low OR high-ratio OR low-ratio) AND Plasma AND resuscitation
Database: Embase Date: 8/5/20 Searcher: Kay Smith & Jill Deaver Intervention: High Plasma ratio resuscitation versus Low Plasma Ratio Resuscitation Filters: Non-medline; articles and reviews only (no conference abstracts) Results: 1	('hemorrhagic shock'/exp OR 'hemorrhagic shock' OR ((h?emorrhagic NEAR/3 shock):ti,ab,kw) OR ((bleeding NEAR/3 shock):ti,ab,kw)) AND ('injury'/exp OR 'injury' OR trauma*:ti,ab,kw OR injur*:ti,ab,kw) AND ('high plasma ratio resuscitation' OR (high AND ('plasma'/exp OR plasma) AND ('ratio'/exp OR ratio) AND ('resuscitation'/exp OR resuscitation))) AND [embase]/lim NOT ([embase]/lim AND [medline]/lim) AND 'review'/it
Database: Clinical Trials.gov July 21, 2020 Searcher: Geeta Malik Intervention: High Plasma ratio resuscitation versus Low Plasma Ratio Resuscitation Results: 3	Trauma OR injury[Other terms] Hemorrhagic Shock [Condition or disease] Resuscitation AND Plasma [Intervention/treatment]
Database: Cochrane Library Date: 8/4/20 Searcher: Kay Smith Intervention: High Plasma ratio resuscitation versus Low Plasma Ratio Resuscitation Results: 1 review (duplicate, removed in EndNote), 3 trials	#1 MeSH descriptor: [Shock, Hemorrhagic] explode all trees98 #2 (hemorrhagic shock):ti,ab,kw (Word variations have been searched) 804 #3 #1 OR #2 804 #4 MeSH descriptor: [Wounds and Injuries] explode all trees 24996 #5 MeSH descriptor: [Accidents] explode all trees 5783 #6 MeSH descriptor: [] explode all trees and with qualifier(s): [injuries - IN] 3299 #7 (injuries):ti,ab,kw (Word variations have been searched) 56774 #8 (trauma):ti,ab,kw (Word variations have been searched) 14648

	#9 #4 OR #5 OR #6 OR #7 OR #8 78799 #10 #3 AND #9 279 #11 MeSH descriptor: [Plasma] explode all trees 972 #12 (plasma):ti,ab,kw (Word variations have been searched) 96914 #13 #11 OR #12 96989 #14 high OR low 361438 #15 (high ratio):ti,ab,kw (Word variations have been searched) 33970 #16 (low ratio):ti,ab,kw (Word variations have been searched) 24724 #17 #14 OR #15 OR #16 363621 #18 (resuscitation):ti,ab,kw (Word variations have been searched) 7719 #19 #10 AND #13 AND #17 AND #18 4
Database: PubMed July 27, 2020 Searcher: Geeta Malik Intervention: High Platelet ratio resuscitation versus Low platelet ratio resuscitation Results: 50 Upated January 2022: Results: 10	("shock, hemorrhagic"[MeSH Terms] OR "hemorrhagic-shock"[Text Word]) AND ((("Wounds and Injuries"[MeSH Terms] OR "injuries"[MeSH Subheading]) OR "Accidents"[MeSH Terms]) OR ("trauma*"[Text Word] OR "injur*"[Text Word])) **AND** (high OR low OR high-ratio OR low-ratio) AND Platelet* AND resuscitation
Database: Embase Date: 8/5/20 Searcher: Kay Smith & Jill Deaver Intervention: High Platelet ratio resuscitation versus Low platelet ratio resuscitation Filters: Non-medline; articles and reviews only (no conference abstracts) Results: 0	('hemorrhagic shock'/exp OR 'hemorrhagic shock' OR ((h?emorrhagic NEAR/3 shock):ti,ab,kw) OR ((bleeding NEAR/3 shock):ti,ab,kw)) AND ('injury'/exp OR 'injury' OR trauma*:ti,ab,kw OR injur*:ti,ab,kw) AND ('high platelet ratio resuscitation' OR (high AND ('platelet'/exp OR platelet) AND ('ratio'/exp OR ratio) AND ('resuscitation'/exp OR resuscitation))) AND [embase]/lim NOT ([embase]/lim AND [medline]/lim)
Database: Clinical Trials.gov July 21, 2020 Searcher: Geeta Malik Intervention: High Platelet ratio resuscitation versus Low platelet ratio resuscitation Results: 3	Trauma OR injury[Other terms] Hemorrhagic Shock [Condition or disease] Resuscitation AND Platelet [Intervention/treatment]
Database: Cochrane Library Date: 8/4/20 Searcher: Kay Smith	#1 MeSH descriptor: [Shock, Hemorrhagic] explode all trees98 #2 (hemorrhagic shock):ti,ab,kw (Word variations have been searched) 804

Intervention: High Plasma ratio resuscitation versus Low Plasma Ratio Resuscitation Results: 1 review (duplicate, removed in EndNote), 2 trials (duplicates, removed in EndNote)	#3 #1 OR #2 804 #4 MeSH descriptor: [Wounds and Injuries] explode all trees 24996 #5 MeSH descriptor: [Accidents] explode all trees 5783 #6 MeSH descriptor: [] explode all trees and with qualifier(s): [injuries - IN] 3299 #7 (injuries):ti,ab,kw (Word variations have been searched) 56774 #8 (trauma):ti,ab,kw (Word variations have been searched) 14648 #9 #4 OR #5 OR #6 OR #7 OR #8 78799 #10 #3 AND #9 279 #11 MeSH descriptor: [Plasma] explode all trees 972 #12 (plasma):ti,ab,kw (Word variations have been searched) 96914 #13 #11 OR #12 96989 #14 high OR low 361438 #15 (high ratio):ti,ab,kw (Word variations have been searched) 33970 #16 (low ratio):ti,ab,kw (Word variations have been searched) 24724 #17 #14 OR #15 OR #16 363621 #18 (resuscitation):ti,ab,kw (Word variations have been searched) 7719 #19 #10 AND #13 AND #17 AND #18 4 #20 MeSH descriptor: [Blood Platelets] explode all trees 1961 #21 (platelet):ti,ab,kw (Word variations have been searched) 27275 #22 #20 OR #21 27275 #23 #10 AND #17 AND #18 AND #22 3
Pre-hospital blood products use	
Database: PubMed July 16, 2020 Searcher: Paul Mussleman Intervention: Pre-hospital blood product use Results: 173 Upated January 2022: Results: 12	(("Shock, Hemorrhagic"[Mesh] OR ("Hemorrhage/mortality"[Mesh] AND shock[tiab]) OR ("Hemorrhage/therapy"[Mesh] AND shock[tiab]) OR hemorrhagic-shock[tiab] OR "hemorrhagic shock"[tiab] OR haemorrhagic-shock[tiab] OR "haemorrhagic shock"[tiab] OR "Hypovolemic shock"[tiab] OR Hypovolemic-shock[tiab] OR "Hypovolaemic shock"[tiab] OR Hypovolaemic-shock[tiab]) AND ("Blood Transfusion"[Mesh] OR ("Plasma"[Mesh] AND (froze*[tiab] OR transfus*[tiab])) OR ("Blood Platelets"[Mesh] AND transfus*[tiab]) OR (blood*[tiab] AND transfus*[tiab]) OR (platelet*[tiab] AND transfus*[tiab]) OR Autotransfusion*[tiab] OR (plasma*[tiab] AND (exchang*[tiab] OR transfus*[tiab])) OR (Erythrocyt*[tiab] AND transfus*[tiab]) OR

	(Leukocyt*[tiab] AND transfus*[tiab]) OR (Lymphocyt*[tiab] AND transfus*[tiab]) OR “packed red blood cells”[tiab] OR “blood product”[tiab] OR "blood products”[tiab] OR (froze*[tiab] AND plasma*[tiab]))) AND ("Infusions, Intravenous"[Mesh] OR ("Sodium Chloride"[Mesh] AND (infus*[tiab] OR intravenous*[tiab] OR IV[tiab] OR drip*[tiab])) OR ("Fluid Therapy"[mesh] AND (infus*[tiab] OR intravenous*[tiab] OR IV[tiab] OR drip*[tiab])) OR ("Isotonic Solutions"[Mesh] AND (infus*[tiab] OR intravenous*[tiab] OR IV[tiab] OR drip*[tiab])) OR ("Hypotonic Solutions"[Mesh] AND (infus*[tiab] OR intravenous*[tiab] OR IV[tiab] OR drip*[tiab])) OR ("Hypertonic Solutions"[Mesh] AND (infus*[tiab] OR intravenous*[tiab] OR IV[tiab] OR drip*[tiab])) OR ("Electrolytes"[Mesh] AND (infus*[tiab] OR intravenous*[tiab] OR IV[tiab] OR drip*[tiab])) OR “Intravenous Infusion”[tiab] OR “Intravenous Infusions”[tiab] OR “Intravenous Drip”[tiab] OR “Intravenous Drips”[tiab] OR “IV Infusion”[tiab] OR “IV Infusions”[tiab] OR “IV Drip”[tiab] OR “IV Drips”[tiab] OR “drip infusion”[tiab] OR “drip infusions”[tiab] OR ((“Sodium Chloride” OR “(22)Na”[tiab] OR “(24)NaCl”[tiab]) AND (infus*[tiab] OR intravenous*[tiab] OR IV[tiab] OR drip*[tiab])) OR ((“fluid therapy”[tiab] OR “fluid therapies”[tiab]) AND (infus*[tiab] OR intravenous*[tiab] OR IV[tiab] OR drip*[tiab])) OR ((“isotonic solution”[tiab] OR “isotonic solutions”[tiab]) AND (infus*[tiab] OR intravenous*[tiab] OR IV[tiab] OR drip*[tiab])) OR ((“crystalloid solution”[tiab] OR “crystalloid solutions”[tiab]) AND (infus*[tiab] OR intravenous*[tiab] OR IV[tiab] OR drip*[tiab])) OR ((“ringer’s lactate”[tiab] OR “ringers lactate”[tiab] OR “Hartmann's Solution”[tiab] OR “hartmanns solution”[tiab] OR “Lactated Ringer's”[tiab] OR “Lactated Ringers"[tiab] OR “ringer’s solution”[tiab] OR “ringers solution”[tiab] OR “ringer solution”[tiab]) AND (infus*[tiab] OR intravenous*[tiab] OR IV[tiab] OR drip*[tiab])) OR ((“normal saline”[tiab] OR (saline[tiab] AND “0.9% NaCl”[tiab])) AND (infus*[tiab] OR intravenous*[tiab] OR IV[tiab] OR drip*[tiab])) OR ((“hypotonic solution”[tiab] OR “hypotonic solutions”[tiab]) AND (infus*[tiab] OR intravenous*[tiab] OR IV[tiab] OR drip*[tiab])) OR ((“hypertonic solution”[tiab] OR “hyperternic solutions”[tiab]) AND (infus*[tiab] OR intravenous*[tiab] OR IV[tiab] OR drip*[tiab])) OR ((“hypertonic saline solution”[tiab] OR “hyperternic saline solutions”[tiab]) AND (infus*[tiab] OR intravenous*[tiab] OR IV[tiab] OR drip*[tiab])) OR (electrolyte*[tiab] AND (infus*[tiab] OR intravenous*[tiab] OR IV[tiab] OR drip*[tiab])))
Database: Embase July 15, 2020	#16 #3 AND #8 AND #14 AND [english]/lim #15 #3 AND #8 AND #14

Searcher: Paul Mussleman Intervention: Pre-hospital blood product use Filters: English only Results: 248 Upated January 2022: Results: 12	#14 #9 OR #12 OR #13 #13 ((intraven* NEAR/3 infus*):ti,ab,kw) OR ((intraven* NEAR/3 drip*):ti,ab,kw) OR ((iv NEAR/3 infus*):ti,ab,kw) OR ((iv NEAR/3 drip*):ti,ab,kw) OR ((drip* NEAR/3 infus*):ti,ab,kw) OR ((('sodium chloride' OR '22na' OR '24nacl') NEAR/3 (infus* OR intravenous* OR iv OR drip*)):ti,ab,kw) OR ((('fluid therapy' OR 'fluid therapies') NEAR/3 (infus* OR intravenous* OR iv OR drip*)):ti,ab,kw) OR ((('isotonic solution' OR 'isotonic solutions') NEAR/3 (infus* OR intravenous* OR iv OR drip*)):ti,ab,kw) OR ((('crystalloid solution' OR 'crystalloid solutions') NEAR/3 (infus* OR intravenous* OR iv OR drip*)):ti,ab,kw) OR ((('ringers lactate' OR 'hartmanns solution' OR 'lactated ringers' OR 'ringers solution' OR 'ringer solution') NEAR/3 (infus* OR intravenous* OR iv OR drip*)):ti,ab,kw) OR (saline:ti,ab,kw AND '0.9% nacl':ti,ab,kw AND (infus*:ti,ab,kw OR intravenous*:ti,ab,kw OR iv:ti,ab,kw OR drip*:ti,ab,kw)) OR (normal*:ti,ab,kw AND saline:ti,ab,kw AND (infus*:ti,ab,kw OR intravenous*:ti,ab,kw OR iv:ti,ab,kw OR drip*:ti,ab,kw)) OR ((('hypotonic solution' OR 'hypotonic solutions') NEAR/3 (infus* OR intravenous* OR iv OR drip*)):ti,ab,kw) OR ((('hypertonic solution' OR 'hypertonic solutions') NEAR/3 (infus* OR intravenous* OR iv OR drip*)):ti,ab,kw) OR ((('hypertonic saline solution' OR 'hypertonic saline solutions') NEAR/3 (infus* OR intravenous* OR iv OR drip*)):ti,ab,kw) OR ((electrolyte* NEAR/3 (infus* OR intravenous* OR iv OR drip*)):ti,ab,kw) #12 #10 AND #11 #11 infus*:ti,ab,kw OR intravenous*:ti,ab,kw OR iv:ti,ab,kw OR drip*:ti,ab,kw #10 'sodium chloride'/exp OR 'fluid therapy'/exp OR 'isotonic solution'/exp OR 'hypotonic solution'/exp OR 'hypertonic solution'/exp OR 'electrolyte'/exp #9 'intravenous drug administration'/exp #8 #4 OR #5 OR #6 OR #7 #7 ((blood* NEAR/3 transfus*):ti,ab,kw) OR (((platelet* OR thrombocyt*) NEAR/3 transfus*):ti,ab,kw) OR autotransfusion*:ti,ab,kw OR ((plasma* NEAR/3 (exchang* OR transfus* OR froze*)):ti,ab,kw) OR ((erythrocyt* NEAR/3 transfus*):ti,ab,kw) OR ((leukocyt* NEAR/3 transfus*):ti,ab,kw) OR ((lymphocyt* NEAR/3 transfus*):ti,ab,kw) OR ((packed NEAR/3 'red blood cells'):ti,ab,kw) OR 'blood product':ti,ab,kw OR 'blood products':ti,ab,kw #6 'thrombocyte'/exp AND transfus*:ti,ab,kw #5 'plasma'/exp AND (froze*:ti,ab,kw OR transfus*:ti,ab,kw OR

	exchang*:ti,ab,kw) #4 'blood transfusion'/exp #3 #1 OR #2 #2 ((hemorrhag* NEAR/3 shock*):ti,ab,kw) OR ((haemorrhag* NEAR/3 shock*):ti,ab,kw) OR ((hypovolem* NEAR/3 shock*):ti,ab,kw) OR ((hypovolaem* NEAR/3 shock*):ti,ab,kw) #1 'hemorrhagic shock'/exp
Database: Clinical Trials.gov July 16, 2020 Searcher: Paul Mussleman Intervention: Pre-hospital blood product use Results: 10	((Hemorrhagic OR haemorrhagic OR Hypovolemic OR Hypovolaemic) AND shock) AND ((blood OR plasma OR platelet OR leukocyte OR erythrocyte) AND transfusion) AND ((intravenous OR IV) AND (infusion OR drip))
Database: Cochrane Library July 1, 2020 Searcher: Paul Mussleman Intervention: Pre-hospital blood product use Results: 23 citations (1 Cochrane review and 22 trials)	#1 MeSH descriptor: [Shock, Hemorrhagic] explode all trees 97 #2 MeSH descriptor: [Hemorrhage] explode all trees and with qualifier(s): [mortality - MO] 676 #3 (shock):ti,ab,kw 10117 #4 #2 AND #3 36 #5 MeSH descriptor: [Hemorrhage] explode all trees and with qualifier(s): [therapy - TH] 1323 #6 (shock):ti,ab,kw 10117 #7 #5 AND #6 81 #8 (hemorrhagic-shock):ti,ab,kw 255 #9 ("hemorrhagic shock"):ti,ab,kw 255 #10 (haemorrhagic-shock):ti,ab,kw 37 #11 ("Hypovolemic shock"):ti,ab,kw 128 #12 (Hypovolemic-shock):ti,ab,kw 128 #13 ("Hypovolaemic shock"):ti,ab,kw 17 #14 (Hypovolaemic-shock):ti,ab,kw 17 #15 ("haemorrhagic shock"):ti,ab,kw 37 #16 #1 OR #4 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 482 #17 MeSH descriptor: [Blood Transfusion] explode all trees 3489 #18 MeSH descriptor: [Plasma] explode all trees 963 #19 (froze* OR transfus*):ti,ab,kw 19943 #20 #18 AND #19 233 #21 MeSH descriptor: [Blood Platelets] explode all trees 1959 #22 (transfus*):ti,ab,kw 16351 #23 #21 AND #22 179 #24 (blood* AND transfus*):ti,ab,kw 13513 #25 (platelet* AND transfus*):ti,ab,kw 3131

	#26 (Autotransfusion*):ti,ab,kw 460 #27 (plasma* AND (exchang* OR transfus*)):ti,ab,kw 3570 #28 (Erythrocyt* AND transfus*):ti,ab,kw 2286 #29 (Leukocyt* AND transfus*):ti,ab,kw 653 #30 (Lymphocyt* AND transfus*):ti,ab,kw 386 #31 (“packed red blood cells”):ti,ab,kw 364 #32 (“blood product”):ti,ab,kw 607 #33 ("blood products"):ti,ab,kw 1116 #34 (froze* AND plasma*):ti,ab,kw 1171 #35 #17 OR #20 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 17396 #36 MeSH descriptor: [Infusions, Intravenous] explode all trees 10199 #37 MeSH descriptor: [Sodium Chloride] explode all trees 2514 #38 (infus* OR intravenous* OR IV OR drip*):ti,ab,kw 171514 #39 #37 AND #38 818 #40 MeSH descriptor: [Fluid Therapy] explode all trees 1656 #41 (infus* OR intravenous* OR IV OR drip*):ti,ab,kw 171514 #42 #40 AND #41 821 #43 MeSH descriptor: [Isotonic Solutions] explode all trees 946 #44 (infus* OR intravenous* OR IV OR drip*):ti,ab,kw 171514 #45 #43 AND #44 465 #46 MeSH descriptor: [Hypotonic Solutions] explode all trees 75 #47 (infus* OR intravenous* OR IV OR drip*):ti,ab,kw 171514 #48 #46 AND #47 36 #49 MeSH descriptor: [Hypertonic Solutions] explode all trees 698 #50 (infus* OR intravenous* OR IV OR drip*):ti,ab,kw 171514 #51 #49 AND #50 272 #52 MeSH descriptor: [Electrolytes] explode all trees 12604 #53 (infus* OR intravenous* OR IV OR drip*):ti,ab,kw 171514 #54 #52 AND #53 1541 #55 ("Intravenous Infusion" OR "Intravenous Infusions" OR "Intravenous Drip" OR "Intravenous Drips" OR "IV Infusion" OR "IV Infusions" OR "IV Drip" OR "IV Drips" OR "drip infusion" OR "drip infusions"):ti,ab,kw 11707 #56 ("Sodium Chloride" OR "(22)Na" OR "(24)NaCl" OR "fluid therapy" OR "fluid therapies" OR "isotonic solution" OR "isotonic solutions" OR "crystalloid solution" OR "crystalloid solutions" OR "ringer’s lactate" OR "ringers lactate" OR "Hartmann's Solution" OR

	"hartmanns solution" OR "Lactated Ringer's" OR "Lactated Ringers" OR "ringer's solution" OR "ringers solution" OR "ringer solution" OR "normal saline" OR (saline AND "0.9% NaCl") OR "hypotonic solution" OR "hypotonic solutions" OR "hypertonic solution" OR "hyperternic solutions" OR "hypertonic saline solution" OR "hyperternic saline solutions" OR electrolyte*):ti,ab,kw 26989 #57 (infus* OR intravenous* OR IV OR drip*):ti,ab,kw 171514 #58 #56 AND #57 11437 #59 #36 OR #39 OR #42 OR #45 OR #48 OR #51 OR #54 OR #55 OR #58 30472 #60 #16 AND #35 AND #59 23
Use of hemostatic adjuncts	
Intervention: TXA Searcher: Kay H. Smith Database: PubMed Date: 6/16/20 Results: 88 Upated January 2022: Results: 69	(("shock, hemorrhagic"[MeSH Terms] OR "hemorrhagic-shock"[Text Word]) AND ((("Wounds and Injuries"[MeSH Terms] OR "injuries"[MeSH Subheading]) OR "Accidents"[MeSH Terms]) OR ("trauma*"[Text Word] OR "injur*"[Text Word]))) AND (("tranexamic acid"[MeSH Terms] OR ("tranexamic acid"[Text Word] OR "TXA"[Text Word])) OR "antifibrinolytic agents"[Pharmacological Action])
Database: Embase Date: 6/19/20 Limits: Non-Medline; articles/reviews only Results: 25 (1 duplicate removed in EndNote from 26 total results) Upated January 2022: Results: 13	('hemorrhagic shock'/exp OR ((h?emorrhagic NEAR/3 shock):ti,ab,kw) OR ((bleeding NEAR/3 shock):ti,ab,kw)) AND ('injury'/exp OR trauma*:ti,ab,kw OR injur*:ti,ab,kw) AND ('tranexamic acid'/exp OR 'tranexamic acid*':ti,ab,kw OR txa:ti,ab,kw OR 'antifibrinolytic agent*':ti,ab,kw) AND [embase]/lim NOT ([embase]/lim AND [medline]/lim) AND ('article'/it OR 'review'/it)
Database: Cochrane Library Date: 6/19/20 Results: 9 (1 review, 8 trials); 2 duplicate trials removed in EndNote, yielding 6 trial results Upated January 2022: Results: 6	#1 MeSH descriptor: [Shock, Hemorrhagic] explode all trees 96 #2 (hemorrhagic shock):ti,ab,kw (Word variations have been searched) 798 #3 #1 OR #2 798 #4 MeSH descriptor: [Wounds and Injuries] explode all trees 24720 #5 MeSH descriptor: [Accidents] explode all trees 5716 #6 MeSH descriptor: [] explode all trees and with qualifier(s): [injuries - IN] 3276

	#7 (injuries):ti,ab,kw (Word variations have been searched) 55947 #8 (trauma):ti,ab,kw (Word variations have been searched) 14451 #9 #4 OR #5 OR #6 OR #7 OR #8 77684 #10 MeSH descriptor: [Tranexamic Acid] explode all trees 996 #11 ("tranexamic acid"):ti,ab,kw (Word variations have been searched) 2634 #12 (TXA):ti,ab,kw (Word variations have been searched) 757 #13 MeSH descriptor: [Antifibrinolytic Agents] explode all trees 731 #14 #10 OR #11 OR #12 OR #13 2846 #15 #3 AND #9 AND #14 9
Database: ClinicalTrials.gov Date: 6/19/20 Results: 2 Upated January 2022: Results: 2	trauma OR injury *[Other terms]*| Hemorrhagic Shock *[Condition or disease]*| Tranexamic acid *[Intervention/treatment]* trauma OR injury *[Other terms]*| Hemorrhagic Shock *[Condition or disease]*| Antifibrinolytic Agents *[Intervention/treatment] [No non-duplicative results]*
<u>Intervention: Fibrinogen</u> Database: PubMed Date: 6/22/20 Results: 146 (58 duplicates removed in EndNote from 204 total results) Upated January 2022: Results: 104	("shock, hemorrhagic"[MeSH Terms] OR "hemorrhagic-shock"[Text Word]) AND ((("Wounds and Injuries"[MeSH Terms] OR "injuries"[MeSH Subheading]) OR "Accidents"[MeSH Terms]) OR ("trauma*"[Text Word] OR "injur*"[Text Word])) AND "Fibrinogen"[MeSH Terms] OR "fibrinogen*"[Text Word] OR "coagulants"[MeSH Terms] OR "hemostatics"[MeSH Terms]
Database: Embase Date: 6/23/20 Results: 15 (10 duplicates removed in EndNote from 25 total results) Upated January 2022: Results: 8	('hemorrhagic shock'/exp OR ((h?emorrhagic NEAR/3 shock):ti,ab,kw) OR ((bleeding NEAR/3 shock):ti,ab,kw)) AND ('injury'/exp OR trauma*:ti,ab,kw OR injur*:ti,ab,kw) AND ('fibrinogen'/exp OR fibrinogen*:ti,ab,kw) AND [embase]/lim NOT ([embase]/lim AND [medline]/lim) AND ('article'/it OR 'review'/it)
Database: Cochrane Library Date: 6/23/20 Results: 11 (1 reviews; 10 trials); [1 duplicate review and 7 duplicate trials removed in EndNote from 19 total results] Upated January 2022: Results: 5	#1 MeSH descriptor: [Shock, Hemorrhagic] explode all trees96 #2 (hemorrhagic shock):ti,ab,kw (Word variations have been searched) 798 #3 #1 OR #2 798 #4 MeSH descriptor: [Wounds and Injuries] explode all trees 24720 #5 MeSH descriptor: [Accidents] explode all trees 5716 #6 MeSH descriptor: [] explode all trees and with qualifier(s): [injuries - IN] 3276

	#7 (injuries):ti,ab,kw (Word variations have been searched) 55947 #8 (trauma):ti,ab,kw (Word variations have been searched) 14451 #9 #4 OR #5 OR #6 OR #7 OR #8 77684 #10 MeSH descriptor: [Fibrinogen] explode all trees 1693 #11 (fibrinogen):ti,ab,kw (Word variations have been searched) 5409 #12 MeSH descriptor: [Coagulants] explode all trees 1756 #13 MeSH descriptor: [Hemostatics] explode all trees 1628 #14 #10 OR #11 OR #12 OR #13 7030 #15 #3 AND #9 AND #14 19
Database: ClinicalTrials.gov Date: 6/23/20 Results: 3 (1 duplicate removed in EndNote from 4 total results)	trauma OR injury [Other terms]| Hemorrhagic Shock [Condition or disease]| Fibrinogen [Intervention/treatment]
<u>Intervention: Prothrombin Complex Concentrate</u> Database: PubMed Date: 6/25/20 Results: 5 (102 duplicates removed in EndNote from 107 total results)	("shock, hemorrhagic"[MeSH Terms] OR "hemorrhagic-shock"[Text Word]) AND ((("Wounds and Injuries"[MeSH Terms] OR "injuries"[MeSH Subheading]) OR "Accidents"[MeSH Terms]) OR ("trauma*"[Text Word] OR "injur*"[Text Word])) AND "factor ix"[MeSH Terms] OR "coagulants"[MeSH Terms] OR "Prothrombin-Complex"[Text Word] OR "PCC"[Text Word]
Database: Embase Date: 6/25/20 Results: 5 (4 duplicates removed in EndNote from 9 total results) Upated January 2022: Results: 5	('hemorrhagic shock'/exp OR ((h?emorrhagic NEAR/3 shock):ti,ab,kw) OR ((bleeding NEAR/3 shock):ti,ab,kw)) AND ('injury'/exp OR trauma*:ti,ab,kw OR injur*:ti,ab,kw) AND ('prothrombin complex'/exp OR 'prothrombin complex':ti,ab,kw OR pcc:ti,ab,kw) AND [embase]/lim NOT ([embase]/lim AND [medline]/lim) AND ('article'/it OR 'review'/it)
Database: Cochrane Library Date: 6/26/20 Results: 2 (1 review – duplicate, removed in EndNote; 2 of 4 trials duplicates, removed in EndNote) Upated January 2022: Results: 2	#1 MeSH descriptor: [Shock, Hemorrhagic] explode all trees96 #2 (hemorrhagic shock):ti,ab,kw (Word variations have been searched) 798 #3 #1 OR #2 798 #4 MeSH descriptor: [Wounds and Injuries] explode all trees 24720 #5 MeSH descriptor: [Accidents] explode all trees 5716 #6 MeSH descriptor: [] explode all trees and with qualifier(s): [injuries - IN] 3276 #7 (injuries):ti,ab,kw (Word variations have been searched) 55948 #8 (trauma):ti,ab,kw (Word variations have been searched) 14452 #9 #4 OR #5 OR #6 OR #7 OR #8 77685 #10 MeSH descriptor: [Factor IX] explode all trees 72 #11 MeSH descriptor: [Coagulants] explode all trees 1756

	#12 ("prothrombin complex concentrate"):ti,ab,kw (Word variations have been searched) 179 #13 ("pcc"):ti,ab,kw (Word variations have been searched) 489 #14 #10 OR #11 OR #12 OR #13 2359 #15 #3 AND #9 AND #14 5
Database: ClinicalTrials.gov Date: 6/26/20 Results: 2 (1 duplicate removed in EndNote from 4 total results) Upated January 2022: Results: 2	trauma OR injury [Other terms]| Hemorrhagic Shock [Condition or disease]| Prothrombin Complex Concentrate [Intervention/treatment]
Intervention: Calcium Database: PubMed Date: 6/26/20 Results: 113 (5 duplicates removed in EndNote from 105 total results) Upated January 2022: Results: 91	("shock, hemorrhagic"[MeSH Terms] OR "hemorrhagic-shock"[Text Word]) AND ((("Wounds and Injuries"[MeSH Terms] OR "injuries"[MeSH Subheading]) OR "Accidents"[MeSH Terms]) OR ("trauma*"[Text Word] OR "injur*"[Text Word])) AND "calcium"[MeSH Terms] OR "calcium"[Text Word]
Database: Embase Date: 6/26/20 Results: 6 (1 duplicates removed in EndNote from 7 total results)	('hemorrhagic shock'/exp OR ((h?emorrhagic NEAR/3 shock):ti,ab,kw) OR ((bleeding NEAR/3 shock):ti,ab,kw)) AND ('injury'/exp OR trauma*:ti,ab,kw OR injur*:ti,ab,kw) AND ('calcium'/exp OR calcium:ti,ab,kw) AND [embase]/lim NOT ([embase]/lim AND [medline]/lim) AND ('article'/it OR 'article in press'/it OR 'review'/it)
Database: Cochrane Library Date: 6/26/20 Results: 5 trials (0 reviews; 3 duplicate trials removed in EndNote from 8 total results) Upated January 2022: Results: 2	#1 MeSH descriptor: [Shock, Hemorrhagic] explode all trees96 #2 (hemorrhagic shock):ti,ab,kw (Word variations have been searched) 798 #3 #1 OR #2 798 #4 MeSH descriptor: [Wounds and Injuries] explode all trees 24720 #5 MeSH descriptor: [Accidents] explode all trees 5716 #6 MeSH descriptor: [] explode all trees and with qualifier(s): [injuries - IN] 3276 #7 (injuries):ti,ab,kw (Word variations have been searched) 55948 #8 (trauma):ti,ab,kw (Word variations have been searched) 14452 #9 #4 OR #5 OR #6 OR #7 OR #8 77685 #10 MeSH descriptor: [Calcium] explode all trees 3404 #11 (calcium):ti,ab,kw (Word variations have been searched) 28960 #12 #10 OR #11 28960 #13 #3 AND #9 AND #12 8
Database: ClinicalTrials.gov	trauma OR injury [Other terms]| Hemorrhagic Shock [Condition or

Date: 6/26/20 Results: 0 Upated January 2022: Results: 1	disease]| Calcium [Intervention/treatment]
Tourniquet use	
Database: PubMed Date: 8/2/20 Results: 59 Upated January 2022: Results: 21	(Tourniquet* [tiab] OR "Tourniquets"[Mesh]) AND (Fatal* [tiab] OR death* [tiab] OR mortalit* [tiab] OR "Mortality"[Mesh] OR "Blood Transfusion"[Mesh] OR blood-transfusion* [tiab] OR "Amputation"[Mesh] OR "Amputation, Traumatic"[Mesh] OR Amput* [tiab] OR ((limb* [tiab] OR extremit* [tiab] OR "Extremities"[Mesh]) AND ("adverse effects" [Subheading] OR "injuries" [Subheading] OR loss [tiab]))) AND (("Shock, Hemorrhagic"[Mesh] OR ("Hemorrhage"[Mesh] AND shock[tiab]) OR hemorrhagic-shock[tiab] OR haemorrhagic-shock[tiab] OR Hypovolemic-shock[tiab] OR Hypovolaemic-shock[tiab]) AND ("Wounds and Injuries"[Mesh] OR "injuries" [Subheading] OR "Accidents"[Mesh] OR trauma*[tiab] OR injur*[tiab] OR polytrauma*[tiab] OR wound*[tiab]))
Database: Embase Date: 8/3/20 Results: 41 Upated January 2022: Results: 28	'(fatal*:ti,ab,kw OR death*:ti,ab,kw OR mortalit*:ti,ab,kw OR 'blood transfusion*':ti,ab,kw OR amput*:ti,ab,kw OR 'mortality'/exp OR 'blood transfusion'/exp OR 'amputation'/exp OR (('limb'/exp OR extremit*:ti,ab,kw) AND ('adverse event'/exp OR 'injury'/exp OR loss))) AND (('hemorrhagic shock'/exp OR ('bleeding'/exp AND shock:ti,ab) OR hemorrhagic-shock:ti,ab OR haemorrhagic-shock:ti,ab OR Hypovolemic-shock:ti,ab OR Hypovolaemic-shock:ti,ab) AND ('injury'/exp OR 'accident'/exp OR trauma*:ti,ab OR injur*:ti,ab OR polytrauma*:ti,ab OR wound*:ti,ab)) AND (tourniquet*:ti,ab OR 'tourniquet'/exp) AND ('article'/it OR 'article in press'/it OR 'review'/it)
Database: Cochrane Library Date: 8/4/20 Results: 1 Upated January 2022: Results: 1	#1 (Tourniquet*):ti,ab,kw 1954 #2 MeSH descriptor: [Tourniquets] explode all trees 515 #3 #1 OR #2 1954 #4 (Fatal* OR death* OR mortalit* OR blood-transfusion* OR Amput*):ti,ab,kw 145010 #5 MeSH descriptor: [Amputation] explode all trees 435 #6 MeSH descriptor: [Amputation, Traumatic] explode all trees

	54 #7 MeSH descriptor: [Blood Transfusion] explode all trees 3502 #8 MeSH descriptor: [Mortality] explode all trees 13007 #9 MeSH descriptor: [Extremities] explode all trees 13948 #10 (limb* OR extremit*):ti,ab,kw 34226 #11 MeSH descriptor: [] explode all trees and with qualifier(s): [adverse effects - AE] 128542 #12 MeSH descriptor: [] explode all trees and with qualifier(s): [injuries - IN] 3299 #13 (loss):ti,ab,kw 75503 #14 #9 OR #10 43312 #15 #11 OR #12 OR #13 198485 #16 #14 AND #15 6546 #17 #4 OR #5 OR #6 OR #7 OR #8 OR #16 153088 #18 MeSH descriptor: [Hemorrhage] explode all trees 14186 #19 (shock):ti,ab,kw 10178 #20 #18 AND #19 234 #21 MeSH descriptor: [Shock, Hemorrhagic] explode all trees98 #22 (hemorrhagic-shock OR haemorrhagic-shock OR Hypovolemic-shock OR Hypovolaemic-shock):ti,ab,kw451 #23 #20 OR #21 OR #22 587 #24 MeSH descriptor: [Wounds and Injuries] explode all trees 24996 #25 MeSH descriptor: [] explode all trees and with qualifier(s): [injuries - IN] 3299 #26 MeSH descriptor: [Accidents] explode all trees 5783 #27 (trauma* OR injur* OR polytrauma* OR wound*):ti,ab,kw 93628 #28 #24 OR #25 OR #26 OR #27 106231 #29 #20 OR #23 587 #30 #28 AND #29 267 #31 #3 AND #17 AND #30 2"
Database: ClinicalTrials.gov Date: 8/4/20 Results: 1 Updated January 2022: Results: 2	trauma OR injury [Other terms]| Hemorrhagic Shock [Condition or disease]| Tourniquet [Intervention/treatment]
Pre-hospital airway and blood pressure management	
<u>Hemorrhagic Shock/Intubation</u>	("shock, hemorrhagic"[MeSH Terms] OR "hemorrhagic-shock"[Text

Database: PubMed Date: 8/7/20 Searcher: Kay Smith Results: 90 Upated January 2022: Results: 24	Word]) AND ((("Wounds and Injuries"[MeSH Terms] OR "injuries"[MeSH Subheading]) OR "Accidents"[MeSH Terms]) OR ("trauma*"[Text Word] OR "injur*"[Text Word])) AND "intubation"[MeSH Terms] OR "chest tubes"[MeSH Terms] OR "intubat*"[Text Word]
Database: Embase Date: 8/7/20 Searcher: Becca Billings Filters: No conference abstracts Results: 169 (54 duplicates removed in EndNote from 223 total results) Upated January 2022: Results: 19	('hemorrhagic shock':exp OR hemorrhagic-shock:ab,ti) AND ((('wounds and injuries surgery':exp OR 'injury'/exp OR 'wound'/exp OR 'accident':exp) OR ('trauma':ab,ti OR 'injur*:ab,ti'))) AND ('intubation'/exp OR 'chest tube'/exp OR 'intubat*':ab,ti OR chest-tube*:ab,ti)
Database: Cochrane Library Date: 8/10/20 Searcher: Kay Smith Results: 1 review, 13 trials (2 duplicates removed in EndNote from 15 total trials)	#1 MeSH descriptor: [Shock, Hemorrhagic] explode all trees 98 #2 (hemorrhagic shock):ti,ab,kw (Word variations have been searched) 804 #3 #1 OR #2 804 #4 MeSH descriptor: [Wounds and Injuries] explode all trees 24996 #5 MeSH descriptor: [Accidents] explode all trees 5783 #6 MeSH descriptor: [] explode all trees and with qualifier(s): [injuries - IN] 3299 #7 (injuries):ti,ab,kw (Word variations have been searched) 56774 #8 (trauma):ti,ab,kw (Word variations have been searched) 14649 #9 #4 OR #5 OR #6 OR #7 OR #8 78799 #10 #3 AND #9 279 #11 MeSH descriptor: [Intubation] explode all trees 5179 #12 MeSH descriptor: [Chest Tubes] explode all trees 256 #13 (intubate):ti,ab,kw (Word variations have been searched) 17995 #14 (intubation):ti,ab,kw (Word variations have been searched) 18001 #15 #11 OR #12 OR #13 OR #14 18726 #16 #10 AND #15 16
Database: ClinicalTrials.gov Date: 8/10/20 Searcher: Kay Smith Results: 1	trauma OR injury [Other terms] | Hemorrhagic Shock [Condition or disease] | intubation [Intervention/treatment] [1 result] trauma OR injury [Other terms] | Hemorrhagic Shock [Condition or disease] | chest tubes [Intervention/treatment] [0 results]
Hemorrhagic Shock/Permissive Hypotension	("shock, hemorrhagic"[MeSH Terms] OR "hemorrhagic-shock"[Text

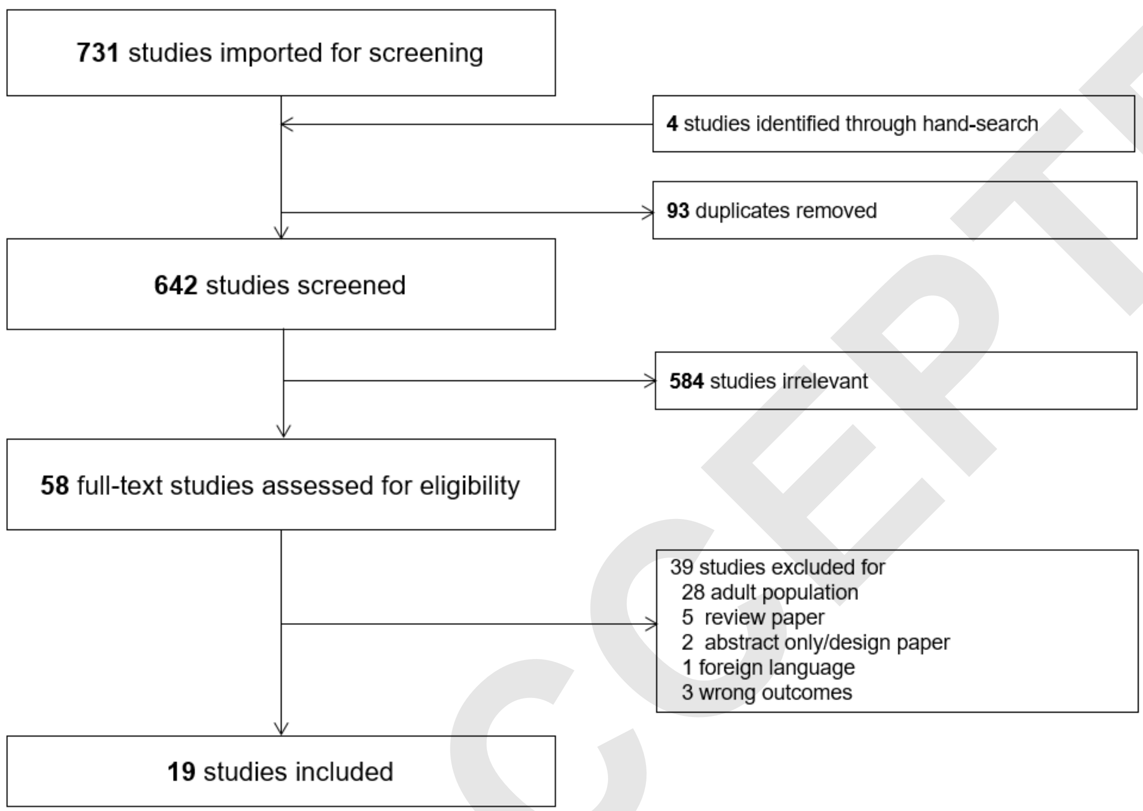
Database: PubMed Date: 8/7/20 Searcher: Kay Smith Results: 184 (3 duplicates removed in EndNote from 187 total results) Upated January 2022: Results: 21	Word]) AND ((("Wounds and Injuries"[MeSH Terms] OR "injuries"[MeSH Subheading]) OR "Accidents"[MeSH Terms]) OR ("trauma*"[Text Word] OR "injur*"[Text Word])) AND ((("hypotension"[MeSH Terms] OR "resuscitation"[MeSH Terms]) OR "hypotension"[Text Word]) OR "resuscitation"[Text Word]) AND ("permissive"[Text Word] OR "hypotensive"[Text Word])
Database: Embase Date: 8/7/20 Searcher: Becca Billings Filters: No conference abstracts Results: 66 (112 duplicates removed in EndNote from 178 total results) Upated January 2022: Results: 5	('hemorrhagic shock':exp OR hemorrhagic-shock:ab,ti) AND ((('wounds and injuries surgery':exp OR 'injury'/exp OR 'wound'/exp OR 'accident':exp) OR ('trauma':ab,ti OR 'injur*:ab,ti'))) AND ¬¬(((‘hypotension’/exp OR ‘resuscitation’/exp) OR ‘hypotension’:ab,ti) OR ‘resuscitation’:ab,ti) AND (‘permissive’:ab,ti OR ‘hypotensive’:ab,ti)
Database: Cochrane Library Date: 8/10/20 Searcher: Kay Smith Results: 1 review, 27 trials (15 duplicates removed in EndNote from 42 trials total)	#1 MeSH descriptor: [Shock, Hemorrhagic] explode all trees98 #2 (hemorrhagic shock):ti,ab,kw (Word variations have been searched) 804 #3 #1 OR #2 804 #4 MeSH descriptor: [Wounds and Injuries] explode all trees 24996 #5 MeSH descriptor: [Accidents] explode all trees 5783 #6 MeSH descriptor: [] explode all trees and with qualifier(s): [injuries - IN] 3299 #7 (injuries):ti,ab,kw (Word variations have been searched) 56774 #8 (trauma):ti,ab,kw (Word variations have been searched) 14649 #9 #4 OR #5 OR #6 OR #7 OR #8 78799 #10 #3 AND #9 279 #11 MeSH descriptor: [Hypotension] explode all trees 2182 #12 MeSH descriptor: [Resuscitation] explode all trees 4897 #13 (hypotension):ti,ab,kw (Word variations have been searched) 17115 #14 (resuscitation):ti,ab,kw (Word variations have been searched) 7719 #15 #11 OR #12 OR #13 OR #14 27604 #16 (permissive):ti,ab,kw (Word variations have been searched) 6209 #17 (hypotensive):ti,ab,kw (Word variations have been searched) 17106 #18 #16 OR #17 23103

	#19 #15 AND #18 17155 #20 #10 AND #19 43
Database: ClinicalTrials.gov Date: 8/10/20 Searcher: Kay Smith Results: 2	trauma OR injury [Other terms] | Hemorrhagic Shock [Condition or disease] | permissive hypotension [Intervention/treatment] [0 results] trauma OR injury [Other terms] | Hemorrhagic Shock [Condition or disease] | hypotensive resuscitation [Intervention/treatment] [2 results]
Conventional coagulation tests or thromboelastography-guided resuscitation	
Intervention: TEG Database: PubMed Date: 7/24/20 Results: 122 Upated January 2022: Results: 17	"shock, hemorrhagic"[MeSH Terms] OR "hemorrhagic-shock"[Text Word] AND "Wounds and Injuries"[MeSH Terms] OR "injuries"[MeSH Subheading] OR "Accidents"[MeSH Terms] OR "trauma*"[Text Word] OR "injur*"[Text Word] AND ((("thrombelastography"[MeSH Terms] OR "thromboelastograph*"[Text Word]) OR "thromboelastometr*"[Text Word]) OR "TEG"[Text Word]) OR (("conventional-coagulation"[Text Word] OR "CCT"[Text Word]) OR ("blood coagulation tests"[MeSH Terms] AND "conventional"[Text Word]))
Database: Embase Date: 7/24/20 Limits: Non-Medline; articles/reviews only Results: 12 (5 duplicates removed in EndNote from 17 total results)	('hemorrhagic shock'/exp OR ((h?emorrhagic NEAR/3 shock):ti,ab,kw) OR ((bleeding NEAR/3 shock):ti,ab,kw)) AND ('injury'/exp OR trauma*:ti,ab,kw OR injur*:ti,ab,kw) AND ('thromboelastography'/exp OR thrombelastogra*:ti,ab,kw OR thromboelastogra*:ti,ab,kw OR 'thrombo elastogra*':ti,ab,kw OR 'teg':ti,ab,kw OR 'blood clotting test'/exp OR ((conventional NEAR/3 (coagulat* OR clotting)):ti,ab,kw) OR 'cct':ti,ab,kw) AND [embase]/lim NOT ([embase]/lim AND [medline]/lim) AND ('article'/it OR 'review'/it)
Database: Cochrane Library Date: 7/24/20 Results: 9 (1 duplicate removed in EndNote from 10 trials)	#1 MeSH descriptor: [Shock, Hemorrhagic] explode all trees97 #2 (hemorrhagic shock):ti,ab,kw (Word variations have been searched) 801 #3 #1 OR #2 801 #4 MeSH descriptor: [Wounds and Injuries] explode all trees 24866 #5 MeSH descriptor: [Accidents] explode all trees 5755 #6 MeSH descriptor: [] explode all trees and with qualifier(s): [injuries - IN] 3289 #7 (injuries):ti,ab,kw (Word variations have been searched) 56411 #8 (trauma):ti,ab,kw (Word variations have been searched) 14572

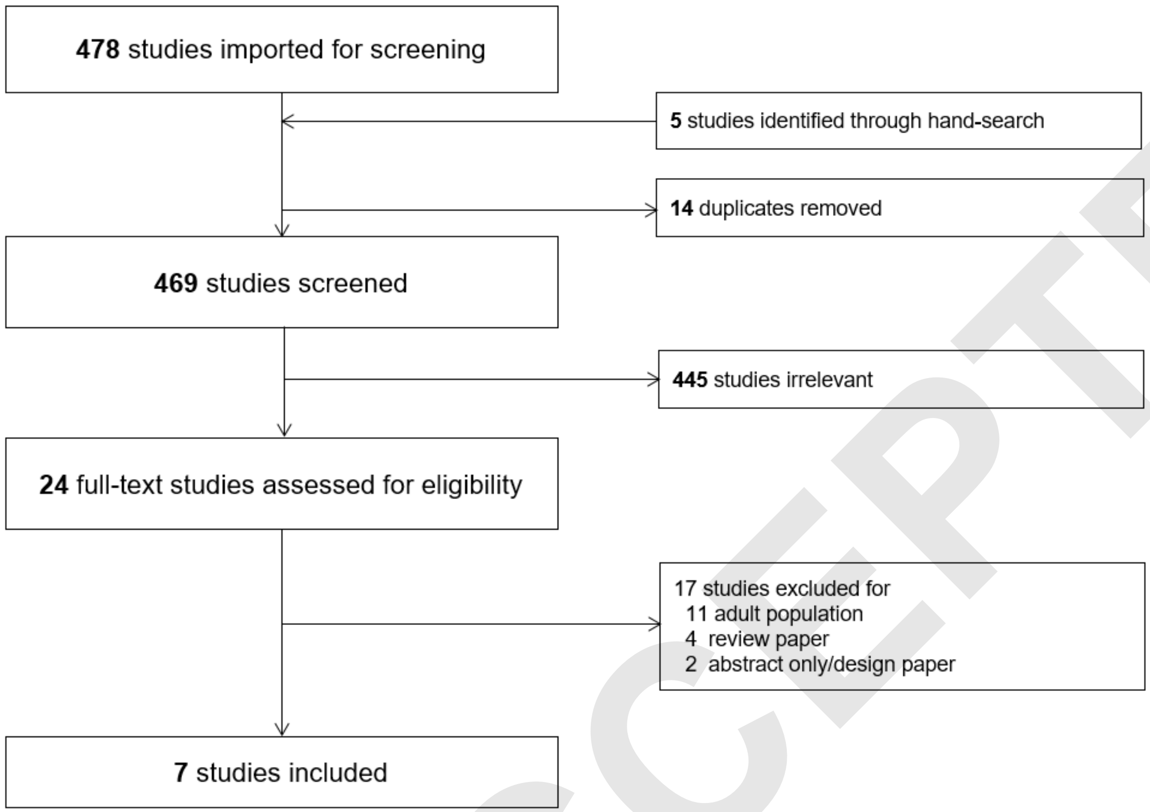
	#9 #4 OR #5 OR #6 OR #7 OR #8 78315 #10 MeSH descriptor: [Thrombelastography] explode all trees 236 #11 ("thromboelastography"):ti,ab,kw (Word variations have been searched) 373 #12 ("thromboelastogram"):ti,ab,kw (Word variations have been searched) 48 #13 (thromboelastometry):ti,ab,kw (Word variations have been searched) 210 #14 (TEG):ti,ab,kw (Word variations have been searched) 349 #15 MeSH descriptor: [Blood Coagulation Tests] explode all trees 2013 #16 (conventional):ti,ab,kw (Word variations have been searched) 59241 #17 (coagulation):ti,ab,kw (Word variations have been searched) 11349 #18 (clotting):ti,ab,kw (Word variations have been searched) 8187 #19 (CCT):ti,ab,kw (Word variations have been searched) 995 #20 #15 OR #17 OR #18 17917 #21 #16 AND #20 1059 #22 #19 OR #21 2049 #23 #10 OR #11 OR #12 OR #13 OR #14 806 #24 #22 OR #23 2783 #25 #3 AND #9 AND #24 10
Database: ClinicalTrials.gov Date: 7/24/20 Results: 2	trauma OR injury [Other terms]| Hemorrhagic Shock [Condition or disease]| thrombelastography [Intervention/treatment] trauma OR injury [Other terms]| Hemorrhagic Shock [Condition or disease]| TEG [Intervention/treatment] trauma OR injury [Other terms]| Hemorrhagic Shock [Condition or disease]| CCT [Intervention/treatment] trauma OR injury [Other terms]| Hemorrhagic Shock [Condition or disease]| conventional coagulation [Intervention/treatment]

Supplemental Figure 1. PRISMA Diagrams for Systematic Reviews

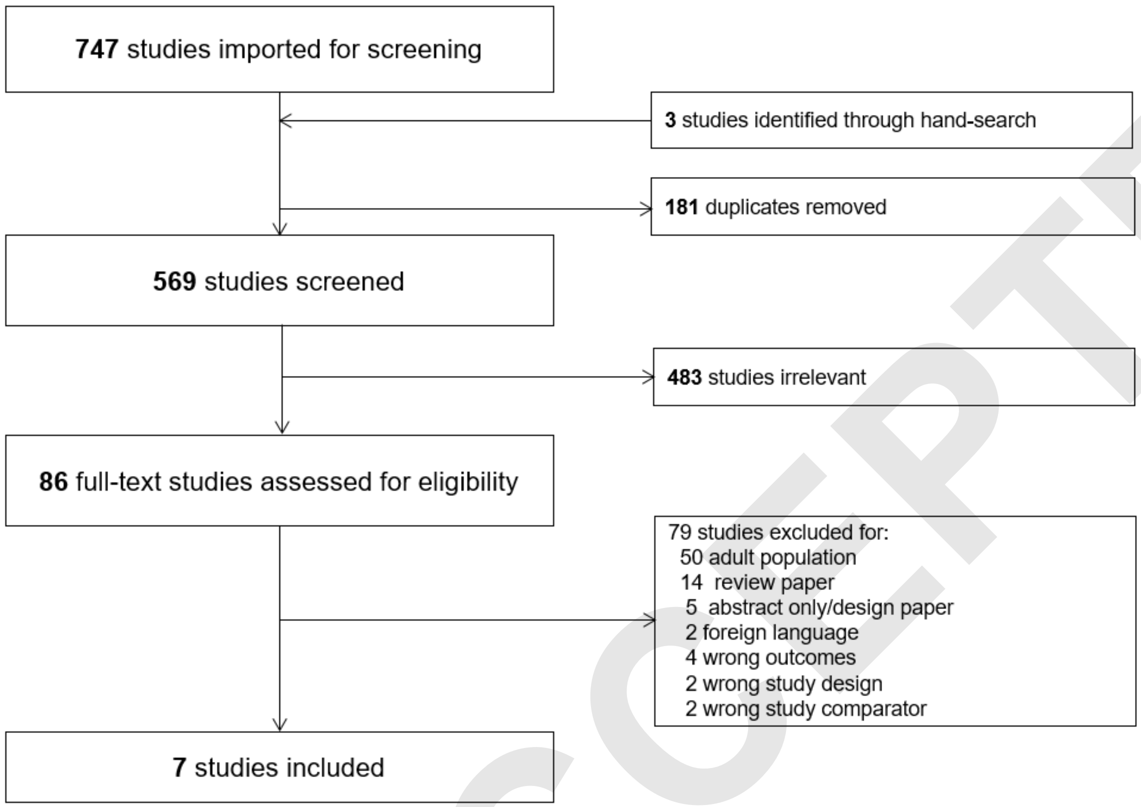
1.A. Blood products and fluid resuscitation for hemostatic resuscitation



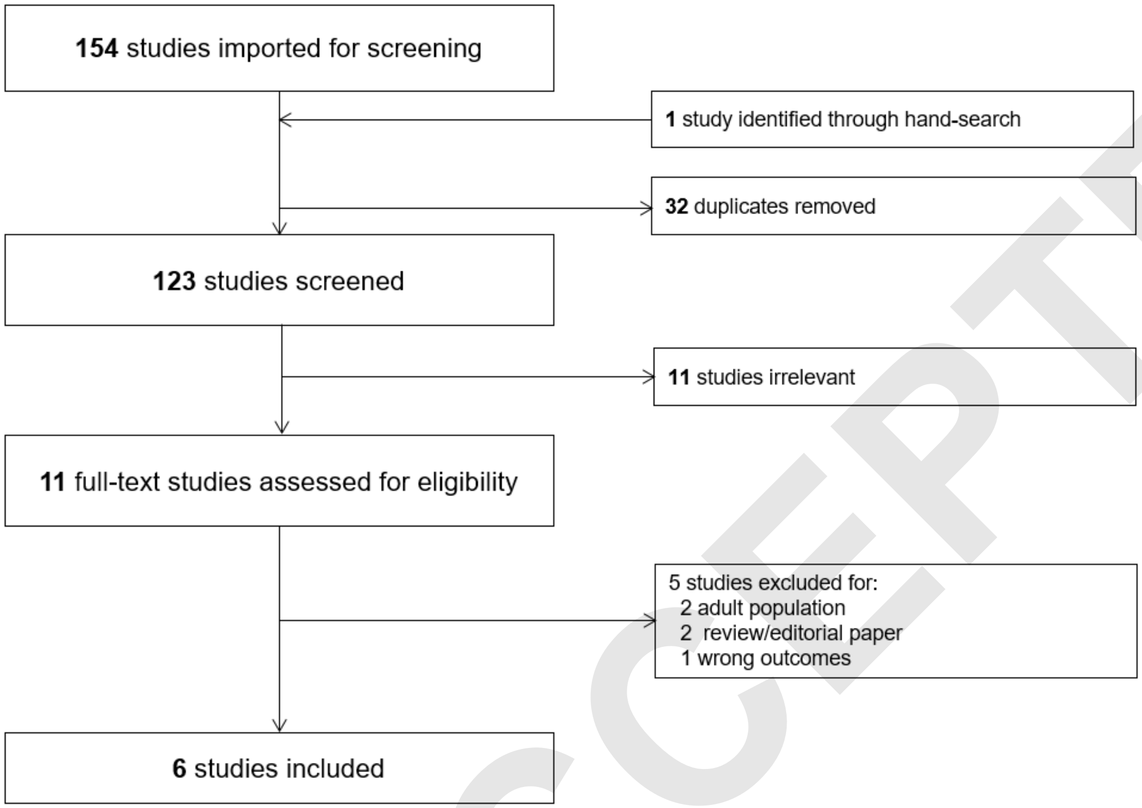
1. B. Utilization of pre-hospital blood products



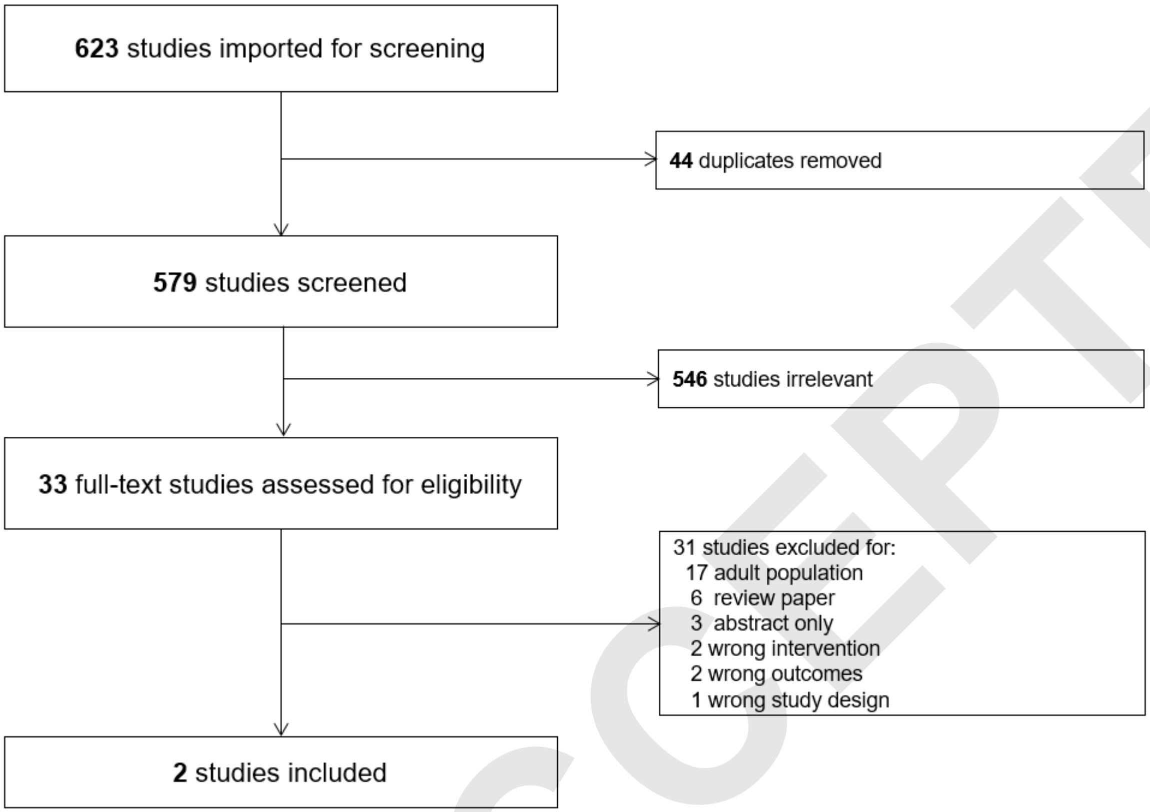
1.C. Use of hemostatic adjuncts



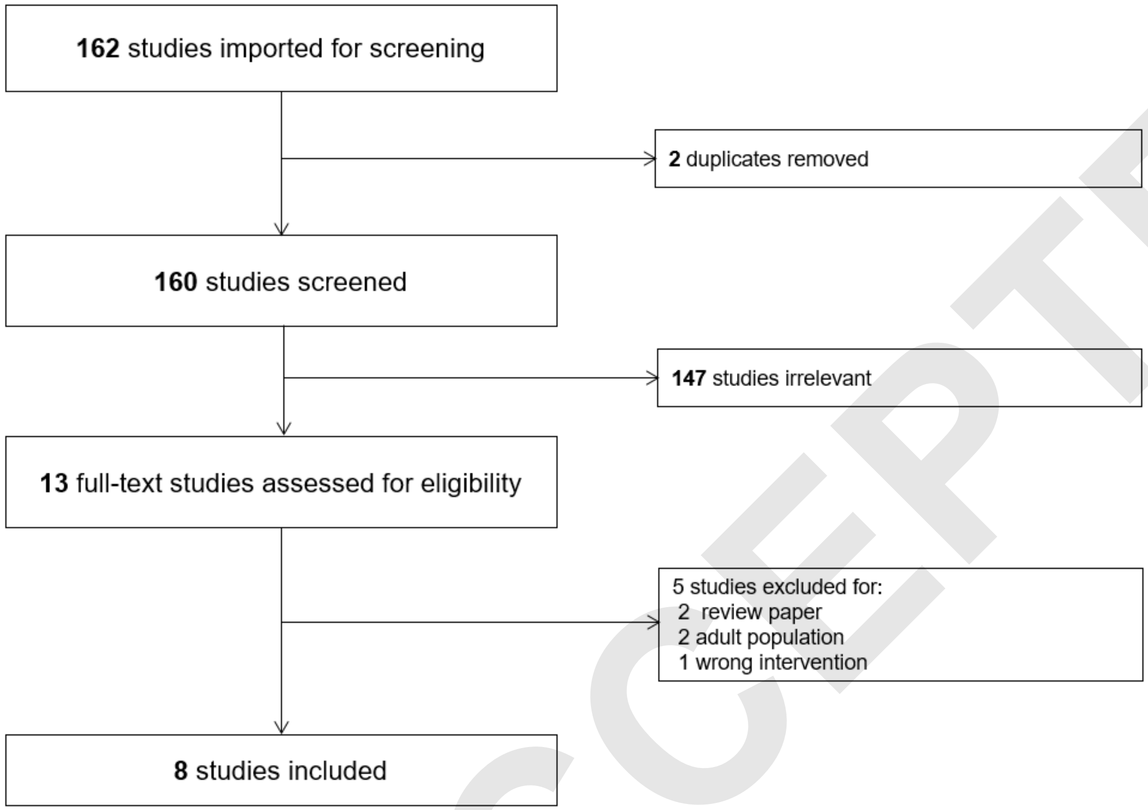
1.D. Tourniquet use



1.E. Pre-hospital airway and blood pressure management



1.F. conventional coagulation tests or thromboelastography-guided resuscitation.



Supplemental Table 3. Articles Included for Blood Products and Fluid Resuscitation for Hemostatic Resuscitation

Publication year	1st author	Study design	Study years	Setting	Sample size (n)	Population / disease	Age ±SD or Median(IQR)	Male	ISS	Intervention ± comparator	Blood products given	Primary outcome	Secondary outcomes	Conclusion	Risk of bias
2019	Cunningham	Retro-spective cohort	2015-2016	Trauma centers (TQIP)	465	Blunt / penetrating trauma	8 yr (2-15)	67 %	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.	Ventilator free days, ICU / hospital length of stay / mortality (38%)	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).	Low
2019	Butler	Retro-spective cohort	2014-2016	Trauma Centers (TQIP)	583	Blunt / penetrating trauma, gunshot / stab wound, other	5 yr (2-10)	60 %	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%)	Ventilator free days, hospital / ICU LOS	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).	Low
2019	Leeper	Retro-spective historical trial	2015-2017	Trauma (Single Center)	22	Blunt / penetrating trauma	8.5 yr	68 %	Mean 26	Cold-stored PLT within whole blood vs.	Whole blood, PLT	Cold-stored whole blood platelet	In-hospital mortality; ICU	Neither posttransfusion platelet	Mod

										conventional warm platelet		function	LOS, Vent days	count (129 x 10^9/L vs. 135 x 10^9/L) nor function (TEG maximum amplitude, 59.5 mm vs. 60.2 mm) differed significantly between cold-stored versus conventional warm PLT.	
2019	Nadler	Retrospective cohort	2013-2018	Trauma registry	33	Patients < 18 yo with trauma treated in the field by advanced life support providers	15 yr (15-17)	79 %	NR	None	Plasma, RBCs	Transfusion related adverse events	Total transfusions and interventions in the field	Freeze dried plasma administration in prehospital scenario feasible for pediatric trauma pts	N/A
2020	Nadler	Retrospective cohort	2018-2019	Trauma registry	8	All Patients treated with LTOWB	25 yr (range: 2-45 yr)	71 %	NR	None	LTOWB	implementation of LTOWB program		LTOWB administration in prehospital scenario feasible for pediatric trauma pts	N/A
2017	Cannon	Retro-spective cohort	2001-2013	Military trauma/DOD	364	Blunt / penetrating trauma, other	8 yr (4-12)	75 %	Mean 17	High (> 1:2) vs. low (< 1:2) plasma/RBC ratio	MT of plasma & RBC	Mortality at 24 hr (18.7%)	Ventilator-free days, ICU / hospital mortality and LOS	No difference in all-cause mortality at 24 hours (high, 8.0% vs low, 9.2%; p = 0.75) and hospital discharge (high,	Low-mod

														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).	
2018	Polites	Pro-spective cohort	2010-2016	Level 1 pediatric trauma centers	208	Blunt / penetrating trauma, gunshot / stab wound, other	5±4 yr	51 %	Median 11 (6, 25)	Crystalloid bolus (20±10 mL/kg)	Plasma, PLT, RBC	Blood product transfusion	Hospital / ICU LOS, in-hospital death, discharge disposition	The likelihood of transfusion increased logarithmically from 11% to 43% for those requiring 2 or more boluses of crystalloid (AUROC: 0.89).	Low-mod
2021	Leonard	Prospective Observational	2014-2018	PICU population with LTB	449 (n=207 trauma)	Trauma, operative, and medical bleeding	10.4 yr (4.7-15.4)	62 %	29 (20-38)	MT	Plasma, PLT, RBC	6h, 24h, and 28 day mortality	ARDS, Sepsis, AKI, ACS	35.7% of death occurred during MT (40.5% trauma); 6 hour trauma mortality: 63% bleeding, 37% CNS injury; 24 hour trauma	Low

														mortality: 56% bleeding, 42% CNS injury; 28 day trauma mortality: 58% CNS injury	
2021	Leeper	Prospective Observational Study	2013-2020	Trauma with MT (single center)	80	Blunt/ penetrating trauma	6 yr (2-12)	56 %	30 (21-38)	LTOWB supplemented with CT vs CT therapy only	LTOWB, Plasma, PLT, RBC	Mortality at 28 days	6 and 72 hr survival, AKI, ICU LOS, Vent days, Transfusion rxn, VTE	Administration of LTOWB during hemostatic resuscitation was independently associated with improved 72 hour and 28 day survival (adj OR=0.23 and 0.41, respectively)	Low
2018	Noland	Multicenter Retrospective cohort	2007-2013	Five Level 1 pediatric trauma centers	110	Blunt/ penetrating trauma	5.9 yr (3-11.4)	60 %	26 (20-37)	RBC: FFP ratio--1:1, 2:1. and 3:1 or greater	Plasma, PLT, RBC	Survival	Hospital LOS, ICU LOS, discharge outcomes	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	Low-Mod
2016	Hwu	Historical control trial	2005-2014	ER	235	Blunt / penetrating trauma	Range (6 groups)4.7 ±6.3 to 11.0 ±6.4	60 %	Range (6 groups) 22 to 35	Before (120 patients) vs after (115) MTP	Plasma, PLT, RBC. MT in	In-hospital mortality (19%)	Blood product use, ICU /	No difference in in-hospital	Low-mod

							yr			implementation.	26 before and 17 after MTP.		ventilator-free days, hospital / ICU LOS.	mortality and secondary outcomes between pre- and post-MTP groups (24% vs. 19%) or MT subgroups (54% vs. 47%).	
2017	Hwu	Retro-spective cohort	2006-2012	ER	38	Blunt / penetrating trauma	6.0 yr (2.8-14.9)	76 %	Mean 33	High (≥1:2) vs. low (<1:2) plasma: RBC (P:R) ratios	MT of plasma & RBC	In-hospital mortality (45.8%)	hospital / ICU LOS	No significant difference in in-hospital mortality (45.8% vs. 64.3%) between high and low P: R ratio at 24 h from injury.	Low-mod
2018	Cannon	Retro-spective cohort	2001-2013	Military trauma/DOD	4,358 (1,377 +Tx, 532 MT)	Blunt / penetrating trauma	9 yr (6-13)	88 %	Mean 9 (4-17)	Early Resusc Practices (2001-2005) vs Late (2006-2013)	PRBC, PLT, FFP, WB	Mortality at 24 hr (18.7%)	Ventilator-free days, ICU / hospital mortality and LOS	Transfusion practices in pediatric combat casualty shifted toward a more hemostatic approach with increased transfusions and MT; Mortality remained stable despite increasing ISS and decreased mortality	Mod

													was demonstrated in MT cohort	
2020	Polites	Pro-spective cohort	2018-2019	Level 1 and 2 pediatric trauma centers	712	Blunt / penetrating trauma, gunshot / stab wound, other	7.6 ±5.7 yr	53 %	Median 9 (2-20)	Patient with +SIPA evaluate outcomes btwn crystalloid and blood product resuscitation	Plasma, PLT, RBC	Survival to discharge	Hospital / ICU LOS, in-hospital death, discharge disposition	In patients with +SIPA, resuscitation with > 1 crystalloid bolus was associate with increased need for transfusion and extended vent days and hospital LOS	Low-mod
2020	Leeper	Retrospective with some prospective data collection	2013-2016	Level I Pediatric Trauma Center	185	Blunt/Penetrating/ Abuse	CT: 8 yr (3-13) WB: 11 yrs (5-14)	65 %	CT: 31 (20-35) WB 27 (19-38)	Components vs LTOWB	Plasma, PLT, RBC, LTOWB	Time to resolution of BD	Product volumes transfused, INR, in-hospital death, ICU LOS, Vent days	Propensity matched cohorts: LTOWB group had faster resolution of base deficit, less coagulopathy following transfusion, and decreased plasma and platelet transfusion volumes	Low
2020	Anand	Retrospective	2017	Trauma centers (TQIP)	135	Blunt/Penetrating	CT: 11.8 +/- 5.3 yrs: WB-CT: 12.2 +/- 4.9 yrs	64 %	32	Component vs. WB and components	Plasma, PLT, RBC, LTOWB	volume transfused at 4-hr and 24-hrs	24 hr mortality, in-hospital mortality, hospital LOS, vent days	Use of WB in pediatric trauma patients is associated with decreased transfusion requiremen	Low

														ts and Vent days compared with CT only	
2022	Hesling	Retrospective	2007-2016	Military Trauma (DOD)	536	Penetrating. Explosive, Blunt trauma	10 yr (5-13)	73 %	17 (13-25)	SMT (>80 ml/kg) vs MT (40-80 ml/kg)	Plasma, PLT, RBC, LTOWB, Cryo	Mortality	Assoc of SMT with injury patterns	SMT patients had higher mortality than MT patients (22% vs 14%); Strong associations btwn abdominal and extremity injuries with SMT	Mod
2020	Schauer	Retrospective	2007-2016	Military Trauma (DOD)	521	Penetrating. Explosive, Blunt trauma	10 yr (5-13)	73 %	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	Vent days	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	Mod
2014	Edwards	Retrospective	2002-	Military Trauma	224 HVT,	Penetrating. Explosive, Blunt	Categories	76 %	Categories	HVT (>70 ml/kg) vs.	Plasma, PLT,	Mortality	Hospital, ICU, vent	Injured children	Mod

			201 2	(DOD)	77 MT	trauma				MT (>40 ml/kg)	RBC, WB		days	requiring LVT or MT did not benefit from resuscitatio n strategy using 1:1 PRBC:Plas ma or WB in terms of survival, hospital, ICU, or vent days; heavy reliance on crystalloid for resuscitatio n resulted in adverse outcomes and increased mortality	

[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; SIPA: Shock Index Pediatric Adjusted; LTB: Life-threatening bleeding; mo: month; mod: moderate; HVT: High volume transfusion; SMT: super massive transfusion; MTP: MT protocol; NR: not reported. OR: odds ratio; CT: component therapy; Cryo: cryoprecipitate; WB: whole blood; LTOWB: Low Titer Group O whole blood

Supplemental Table 4. Articles Included for Utilization of Pre-hospital Blood Products

Year Pub	1st author	Study design	Study Years	Setting	Sample size (n)	Population / disease	Age ±SD or (IQR)	Male	ISS	Prehospital Blood products Given	# of patients with Prehospital Blood Products	Primary outcome[a]	Secondary outcomes[a]	Conclusion	Risk of bias
2018	Polites	Prospective cohort	2010 - 2016	Level 1 PTCs	208	Blunt / penetrating trauma, gunshot / stab wound, other	5 ± 4 yr	51%	Median 11 (6, 25)	No, just Crystalloid bolus (20±10 mL/kg)	0	Blood product transfusion	Hospital / ICU LOS, in-hospital death, discharge disposition	The likelihood of transfusion increased logarithmically from 11% to 43% for those requiring 2 or more boluses of crystalloid (AUROC: 0.89).	Mod
2020	Polites	Prospective cohort	2018 - 2019	Level 1 and 2 PTCs	712	Blunt / penetrating trauma, gunshot / stab wound, other	7.6 ±5.7 yr	53%	Median 9 (2-20)	Yes, patients with +SIPA evaluate outcomes between crystalloid and blood product resuscitation	6	Survival to discharge	Hospital / ICU LOS, in-hospital death, discharge disposition	In patients with +SIPA, resuscitation with > 1 crystalloid bolus was associate with increased need for transfusion and extended vent days and hospital LOS	Low - mod
2020	Nadler	Retrospective cohort	2018 - 2019	Trauma registry	8	All Patients treated with LTOWB	25 (range : 2-45 yr)	71%	NR	Yes, LTOWB	8	implementation of LTOWB program		LTOWB administration in prehospital scenario feasible for pediatric trauma pts	N/A
2017	Fahy	Retrospective cohort	2002 - 2014	Pre-hospital	28 total 16 trauma.12 non-trauma	Trauma and non-trauma patients transfused during transport	8.9 ± 7 yr	54%	Mean 24 (9-66)	Yes, PRBC and plasma	16	Safety	Mortality (14%)	Prehospital transfusions of blood products in pediatric patients were	Mod - high

														safe.	
2015	Geeraedts	Retrospective cohort	1995 - 2009	Level 1 trauma center Australia	941	>16 yo, SBP < 90 mmHG, blunt/penetrating trauma	NA	74%	13 (1-75)	Yes, only 1.6% of population	1.6%	Mortality at 24 hrs (7.2%)	Pre-hospital Fluid level (by volume)	Pre-hospital fluid volumes were associated with a decreased likelihood of shock, however fluid volume of > 1 L associated with increased likelihood of blood transfusion in ER	Mod
2021	Van Dijck	Retrospective cohort	2011 - 2019	Level 1 PTC	17	Patients < 18 yo receiving BPs in transport	10.5 (1-17)	53%	30 (9-50)	Yes	17	Mortality	Coag indices, ICU LOS, Hosp LOS	17 cases (matched with pts from pre-airlift transfusion era) received less in flight crystalloid, had higher fibrinogen levels, and shorter time to normal INR	Mod - High
2022	Shirek	Retrospective Cohort	2009 - 2019	Level 1 PTC	38	Patients < 18 yo receiving blood products in transport	7.5 (2.1-11.5)	60%	29 (21-43)	Yes	38	Indications, Safety, outcomes	Tx rxn, AKI, DVT, Sepsis, Vent days, Hosp LOS	38 cases (matched with pts of similar age to pre-transfusion in transport era); admin of blood to pediatric trauma patients prior to PTC arrival is safe, transiently improves	Mod

														markers of shock, and is not associated with adverse outcomes	

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

Abbreviations: AKI: acute kidney injury; Coag: Coagulation; DVT: deep venous thrombosis; PLT: platelets; PRBC: packed red blood cells; AUROC: area under receiver operating curve; ER: Emergency Room INR: international normalized ratio; IQR: interquartile range (25th and 75th quartile); ISS: injury severity score; LOS: length of stay; LTOWB: Low Titer Group O Whole Blood; MT: massive transfusion; MTP: MT protocol; NA: not available; PTC: Pediatric Trauma Center; PICU: pediatric intensive care unit; SBP: systolic blood pressure; Tx rxn: Transfusion Reaction; U: units; yr: years; yo: years old;

Supplemental Table 5. Articles Included for Use of Hemostatic Adjuncts

Year Pub	1st author	Study design	Study Years	Setting	Sample size (n)	Population / disease	Age ±SD or (IQR)	Male	ISS	Adjunct, % patients given adjunct	Overall Mortality	Primary outcome[a]	Secondary outcomes[a]	Conclusion	Risk of bias
2014	Eckert	Retrospective cohort	2008 - 2012	Military trauma (JT Registry)	766	Blunt / penetrating trauma (73%)	11 +/- 5 yrs	88%	10 +/- 9	TXA, 9%	9%	Mortality	Discharge Neuro status, Assoc of TXA in two transfusion groups (MT, LVT)	TXA group was more severely injured, had higher ISS, lower GCS, and more lively to have penetrating or severe abdominal or ext trauma. Adjusted analysis showed TXA to be independently assoc with reduced mortality (OR, 0.27; 0.85-0.89; p=0.03). Propensity match (3:1) model when adjusted for BP ratio showed reduced mortality in TXA patients that received a 1:1 ratio versus those with ratio higher than 1:1 in MT and LVT groups.	Low
2021	Spinella	Prospective cohort	2014 - 2018	24 peds medical centers	449	34% trauma, 46% operative, 20% medical LTB	7 yrs (2-15)	55%	NR	TXA/ EACA, 12%	6h: 15% 24h: 22% 28d:38 %	6, 24h survival	28 d survival	Antifibrinolytics were independently associated with decreased 6h	Low

														and 24 h mortality when used early (1-2 hrs) of development of LTB. Death due to bleeding 6hr post hemorrhage was reduced	
2019	Thompson	Retrospective cohort	2011 - 2019	Level 1 PTC	48	Blunt (79%)/ penetrating	14 yrs (7-15)	71%	31 (24 - 46)	TXA, 60%	31%	Survival to d/c, thrombosis complications	Surgical intervention, BT in first 24 hrs, type and vol of BP admin	No mortality difference btwn TXA and no TXA group. No thrombosis difference btwn groups.	High
2020	Karube	Retrospective cohort	2015 - 2019	Level 1 PTC	24 (22 peds)	Trauma (48%). Operative bleeding, Medical bleeding	13 yrs (2-23)	46%	NR	PCC	37%	Safety, outcomes	INR improvement	Improvement of INR following PCC admin: 5 pts (21%) developed DVT, all CVL associated; No PE	High
2018	Maeda	Retropective cohort (administrative data)	2010 - 2014	Japanese Hospitals	1,914 matched pairs	Trauma patients	7 yrs (4-9)	65%	NR	TXA	13% TXA group; 18% Ref group	Assoc btwn TXA and adverse effects	In hospital mortality	Propensity matched analysis demonstrated significantly higher proportion of seizures in TXA group (0.37% vs 0%); no diff in mortality	High
2020	Hamele	Retrospective cohort	2006 - 2013	Military (DOD)	507 Peds patients with MT	Blunt/penetrating/Blast trauma	9 yrs (5-13)	74%	17 (11 - 26)	TXA	17.4 overall; 8.5% TXA group; 18.3% no TXA	In hospital mortality	24-hr mortality, hospital free days, vent free days, ICU free days	Use of TXA in pediatric patients with combat trauma requiring MT trended toward a significant improvement in in-hospital mortality (p=0.055)	Mod
202	Nishijima	Pilot	2018	4 Level	31	Blunt/penetrating	10.7+/	71%		TXA	0%	Feasibility	Clinical	Confirmed	N/A

2		Randomized Trial	- 2020	1 PTC		trauma	- 5 yrs						outcomes	feasibility of large-scale randomized trial using EFIC	

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

Abbreviationss: NR: not reported; TXA: tranexamic acid; MT: massive transfusion; LVT: Large volume transfusion; ext: extremity; LTB: Life threatening bleeding; EACA: aminocaproic acid: d/c: discharge; ISS: injury severity score; BT: blood transfusions; BP: blood product; mo: month; mod: moderate; MT: massive transfusion; MTP: MT protocol; NA: not available. OR: odds ratio; PTC: Pediatric Trauma Center; PCC: prothrombin complex concentrate; yrs: years.

Supplemental Table 6. Articles Included for Tourniquet Use

Year Pub	1st author	Study design	Study Years	Setting	Sample size (n)	Population / disease	Age ±SD or (IQR)	Male	ISS	# TKT use,% TKT use, Avg time	Overall Mortality	Primary outcome[a]	Secondary outcomes[a]	Conclusion	Risk of bias
2015	Kragh	Retrospective cohort	2001 - 2008	Military	1,413	Blunt/penetrating trauma	Median age:24 yrs	NR	Median17	NA	12% TKT group; 11% non-TKT groups	mortality		Comparison of casualties in TKT use vs. non-TKT use with Propensity score matching and direct comparison in TKT vs. no TKT group; TKT use was associated with more profound shock and transfusion requirements, yet those who received TKT had similar survival to those of comparable, transfused casualties who did not have TKT	Low
2014	Ode	Retrospective cohort	2012 - 2013	Level 1 ATC & PTC	56	Trauma (82%)/Other bleeding	NR	NR	9 (4-75)	42%, 72 min (16-241)	5.4% (8.3% TKT, 3.1% non-TKT)	Effects of TKT on hemorrhage control and outcomes when used by EMS	Patient outcomes following appropriate and inappropriate use	TKT patients had higher incidence of shock, vascular injury, hospital admission, hemorrhage control surgery, and BT; No complications in TKT	Mod

														patients related to tourniquet use. Civilian and prehospital personnel use of TKT for uncontrolled hemorrhage is justifiable and poses minimal risks. Standardized training is needed	
2009	Kragh	Prospective observational	2006	Military	232 (9 peds)	Blunt/Penetrating trauma	28 yr (4-70)	95%	10 (1-75)	428 TKT, 309 limbs, 8% of total trauma pop	13%	Determine if TKT use saves lives	TKT adverse outcomes	TKT use when utilized prior to shock is strongly assoc with saved lives; prehospital use of TKT associated with saved lives; 1.7% risk nerve palsy and no amputations related to TKT use	Mod
2012	Kragh	Retrospective cohort (Registry)	2003-2009	Military	88	Blunt/Penetrating trauma	11 yr (4-17)	82%	13 (1-75)	100%, pediatric patients with TKT only	7%	Survey study		Similar survival rates between pediatric and adult studies; primary indication for TKT were ext wounds with possible exsanguination; 7% rate of unindicated TKT in children; deaths occurred in children with	Mod

														lower ISS than would be predicted	
2011	Kragh	Prospective observational	2008	Military	499	Military trauma	29 yrs (16 pts children)	96%	NR	862 tourniquets applied, 651 limbs	13%	Morbidity/Mortality		Overall, 90% survival when TKT applied before shock vs. 18% survival when TKIT placed after shock; TKT use in absence of shock was associated with survival and prehospital TKT use was associated with survival; Morbidity rate (palsy 1.6%; Limb shortening 0.4% in TKT patients	Low
2015	Sokol	Retrospective cohort (Registry)	2004 - 2012	Military	766 total, only 82 PHI-C	Military Trauma	11 yrs	94%	58% 1-15; 33% 16-25; 7% 26-50; 2% 51-75	47 tourniquets applied	12%	Epidemiology of pediatric PHI	negative and positive impact of PHIs	82 patients had PHI related to circulation. Of 125 patients deemed worthy of PHI, 47 patients had tourniquet placed. LE amputations with tourniquets placed received less IVF and decreasing trend in blood product requirements. UE amputations	

														showed no differences with or without tourniquet placement.	

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

Abbreviations: TKT: emergency tourniquet; NR: not reported; MT: massive transfusion; ext: extremity; d/c: discharge; ISS: injury severity score; BT: blood transfusions; BP: blood product; min: minutes; MT: massive transfusion; MTP: MT protocol; NA: not available.; PTC: Pediatric Trauma Center, PHI-pre-hospital interventions; PHI-C pre-hospital interventions related to circulation, including tourniquets; UE and LE-Upper and Lower Extremity

Note: Several of these articles had pediatric patients in a mixed adult population for which the pediatric patients outcomes could not be separated out.

Supplemental Table 7. Articles Included for Pre-hospital Airway and Blood Pressure Management

Pub Year	1st author	Study design	Study years	Setting	Sample size (n)	Population / disease	Age ±SD or (IQR)	Male	ISS	Intervention ± comparator	Blood products given	Primary outcome[a]	Secondary outcomes[a]	Conclusion	Risk of bias
2012	Duke	Retrosp cohort	2007-2011	Level 1 trauma center	307 (132 RFR, 175 SFR)	Penetrating Torso injuries with SBP < 90 mmHg	RFR: 26 +/- 13; SFR: 28+/-15	86%	29 +/- 7	SFR vs. RFR	Plasma, PRBCs, Platelets	Mortality: RFR 21% vs. 37%	Hospital LOS, OR mortality, TICU mortality	RFR in patients managed with DCR for hypotensive trauma patients with penetrating torso injury conveys an overall and early intraoperative survival benefit	Mod
2015	Geeraedts	Retrosp cohort	1995-2009	Level 1 trauma center (Australia)	941	>16 yo, SBP < 90 mmHG, blunt/penetrating trauma	NR	74	13 (1-75)	NR	Not described	Mortality at 24 hrs (7.2%)	Pre-hospital Fluid level (by volume)	Pre-hosp fluid volumes were associated with a decreased likelihood of shock, however fluid vol of > 1 L associated with increased likelihood of blood transf in ED	Mod

Abbreviations: Retrosp: Retrospective; RFR-restrictive fluid resuscitation (<150 ml crystalloid); SFR-standard fluid resuscitation (≥150 ml crystalloid); SBP: systolic blood pressure; FFP-fresh frozen plasma; PRBCs-packed red blood cells; OR:operating room; TICU: Trauma Intensive Care Unit; DCR: damage control resuscitation; L-liter; transf: transfusion; ED :Emergency Department; NR: Not reported.

Supplemental Table 8. Articles Included for Conventional Coagulation Tests or Thromboelastography-guided Resuscitation

Publication year	1st author	Study design	Study years	Setting	Sample size (n)	Population / disease	Age ±SD or (IQR)	Male	ISS	Purpose	Time of labs	Primary outcome[a]	Secondary outcomes[a]	Conclusion	Risk of bias
2021	Phillips	Retro-spective cohort	2015 - 2018	Level 1 and 2 PTC	117 (39 with MT, 78 no MT)	Blunt / penetrating trauma with and without MT	12.4 yrs +/- 7.3 with MT; 14.9 yrs +/- 3.9 with no MT	79 %	30 +/- 13 with MT; 20 +/- 16 with no MT	Compare TEG in MT vs. without MT	TEG within 2 hours of admit	TEG diff btwn MT and no MT.	Total vent days, ICU LOS, hosp LOS, mortality	Pediatric patient who undergo MT are more likely to have lower alpha angles (35.9% vs. 15.4%, p=0.023), MA (43.6% vs. 10.3%, p,0.001) and lower platelet counts (165 vs 281, p<0.001)	Mod
2017	Leeper	Prospective observational	2015 - 2017	Level 1 PTC	83	Blunt / penetrating trauma, abuse, hanging/ drowning	8 yrs (4-12)	68 %	22- (13-34)	Trend fibrinolysis, determine influence of TBI, and MT on fibrinolysis	95 min (70-120 mins)	Fibrinolysis group over time	Head injury TEG characteristics; MT TEG characteristics	Most common fibrinolytic state over time was shutdown (44%), followed by normal (39%), and HF (17%). TBI patients most likely to be in shutdown with sign lower LY30 than non-TBI. For MT group, 50% were in SD on arrival and those in HF (31%) corrected	Mod

														with BPs and without TXA.	
2018	Deng	Retro-spective cohort	2007 - 2017	Six Chinese Level 1 PTCs	366	Blunt trauma (excluded isolated TBI)	NR	40 %	12+/- 7.6	Propensity matched cohort of ROTEM guided resuscitation vs CCT resuscitation	ROTEM 21.5 mins vs. CCT 47.5 mins (p<0.001)	Evaluate ability of resuscitation and reducing BP use in ROTEM vs CCT guided resuscitation	Hospital LOS	Reduction in time of first lab results and transfusion of BP with ROTEM guided hemostatic resuscitation. ROTEM guided resuscitation group had a lower % of patients with coagulopathy after 24 hours, received less FFP transfusions and had a shorter hospital LOS.	Low
2019	Cunningham	Retro-spective cohort	2014 - 2018	Level 1 PTC	90	Blunt and penetrating trauma	11yrs (4-15)	64 %	17 (9-26)	Identify clinically significant ROTEM parameters and evaluate prognostic ability of ROTEM	On admission	Need for PRBC transfusion	In hospital mortality and disability at discharge	Coagulation dysfunction on ROTEM correlates with CCTs and is associated with poor outcomes in children; Proposed thresholds for specific product transfusions based on ROTEM parameters	Mod
2021	Stevens	Retrospective cohort	2015 - 2019	Level 1 PTC and	64	Blunt trauma with solid organ injury	13.3 yrs +/- 4.6	67 %	32 +/- 14	Evaluate TEG guided	NR	Determine correlations btwn TEG-	Compare TEG guided resusc and	Severely injured pediatric	Mod - Hig

				Level 2 PTC						resuscitation in pediatric patients with BSOIs		directed resusc and BP administration in patients with BSOIs	outcomes btwn two centers	trauma patients with BSOIs are coagulopathic on presentation (32%); No diff btwn two centers; TEG-guided resusc of platelets was assoc with decreased hosp LOS and TEG-guided resusc of cryoprecipitate was assoc with a decreased odds of mortality	h
2014	Ryan	Prospective observational	2009 - 2011	Single PTC	22	Blunt/penetrating trauma	6.5 yrs (8 mo-14 yrs)	64 %	9	Evaluate coagulopathy of pediatric trauma patients on admission vs uninjured control group	On admission (no time given)	Comparison of TEG profiles btwn pediatric trauma patients and uninjured elective surgery patients	None	PT was significantly more elevated in pediatric trauma group but no patients coagulopathic upon admission; Trauma group had shorter R and K times and greater alpha angles compared to controls (all p<0.001); D-dimer was significantly more elevated in trauma patients	High

2021	Phillips	Retrospective cohort	2010 - 2020	Level 1 PTC	41 (21 abuse, 20 trauma only)	Abuse, blunt/penetrating trauma	Abuse: 0.5 yrs (0.4, 1.5 yrs); Trauma: 6 yrs (2.5, 8)	NR	Abuse: 17 (9.5, 25); Trauma: 28 (18, 46)	Evaluate differences in TEG between abuse vs. accidental trauma	On admission	TEG differences btwn groups	NR	Abused children showed a hypercoagulable pattern on TEG compared to accidental trauma; shorter R time (67% vs. 30%, p=0.04) and increased alpha angle (47% vs)5, p=0.001); in MV model, only abnormal alpha angle was assoc with abuse and abnormal MA was assoc with mortality	Mod
2013	Vogel	Retrospective cohort	2009 - 2011	Single Level 1 PTC	86	Blunt/penetrating trauma	8 yrs (3, 12)	67 %	21 (9,33)	Evaluate use of rTEG in pediatric trauma patients	On admit	Correlate admission rTEG with CCT	Predict outcome: need for early BPs and lifesaving interventions	Admission rTEG correlates with CCTs and predicts early transfusion, early LSI, and outcomes in pediatric trauma MA was predictive of early LSI	Mod

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

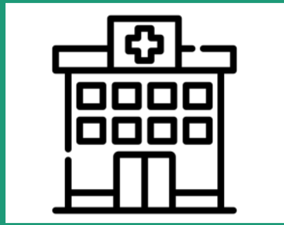
Abbreviations: yrs-years; PTC-pediatric trauma center; MT: massive transfusion; TEG: thromboelastography; diff: differences; ICU: intensive care unit; LOS: length of stay; hosp: hospital; MA: maximum amplitude; min(s): minute(s); LY30-lysis at 30 minutes; HF: hyperfibrinolysis (LY30 ≥3%); BPs: blood products; TXA: tranexamic acid; NR: not reported; BSOIs: blunt solid organ injuries; resusc: resuscitation; mo: months; CCTs: conventional coagulation tests (PT, PTT, INR); LSI: life saving interventions; rTEG: rapid thromboelastography

Pediatric Traumatic Hemorrhagic Shock Consensus Conference Recommendations

Pediatric Traumatic Hemorrhagic Shock

- ✓ Common/preventable cause of death
- ✓ Limited pediatric literature detailing evidence based management

16 multidisciplinary experts systematically evaluated literature from six subtopics



2 Clinical Recommendations, 14 Expert Consensus statements and 5 Good Practice statements for the care of pediatric trauma patients in hemorrhagic shock

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