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RESUSCITATION IN TRAUMA (J SPERRY AND M NEAL, SECTION EDITORS)

Pediatric Trauma Resuscitation Practices

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Abstract

Purpose of Review Trauma is the leading cause of death in children. Hemorrhagic shock is a cause of preventable mortality. Early recognition and treatment of hemorrhagic shock and coagulopathy is essential. This chapter will review current literature on pediatric trauma resuscitation.

Recent Findings.

Current pediatric literature supports limiting crystalloid administration and early use of blood products to resuscitate children in hemorrhagic shock. Both balanced and viscoelastic monitoring–guided resuscitations have been associated with improved outcomes in children; however, data is limited. Utilization of whole blood for pediatric trauma resuscitation is safe and efficient and associated with improved outcomes compared to components. Tranexamic acid may be associated with a survival advantage in injured children.

Summary There has been much progress in the field of pediatric trauma resuscitation, but daily clinical practice still primarily relies on adult data. Ongoing high-quality data is needed to clearly define and optimize hemostatic resuscitation practices in children with hemorrhagic shock.

Keywords Pediatric trauma · Pediatric blood product resuscitation · Whole blood · Viscoelastic monitoring · Tranexamic acid

Introduction

Trauma is the leading cause of mortality in young adults and children, accounting for more than 60% of all pediatric deaths in 2016 [13]. Hemorrhagic shock is the most common cause of preventable mortality in both civilian and combat settings [14, 18, 32]. Adult trauma resuscitation practices have been driven by research, but pediatric specific data remain limited [30, 46].

Children are not little adults; they have different injury patterns, with less hemorrhagic shock and penetrating trauma, higher morbidity from traumatic brain injuries (TBI), and different blood volume and body size ratios [17, 31, 51, 52, 55]. Infants and children have higher circulating blood volumes by weight than adults, so dosing of blood products and hemostatic adjuncts must be weight-based [50]. Early recognition of hemorrhagic shock, coagulopathy, and need for transfusion is of vital importance in severely injured children. Unlike adults, children have a physiologic reserve to maintain normotension even to the verge of circulatory collapse [50]. Hypotension is a sign that an injured child is in extremis and should be aggressively resuscitated. One study found that pediatric trauma patients who were hypotensive on arrival to the emergency department were 13 times more likely to die compared to normotensive patients [33, 35].

Current hemostatic resuscitation practices in children are largely based on adult studies. However, there is a growing body of literature in combat and civilian cohorts allowing for better understanding of hemorrhagic shock, trauma-induced coagulopathy (TIC), damage control resuscitation, and transfusion practices in children.

This chapter will discuss the current literature on key aspects of pediatric trauma resuscitation, including crystalloid utilization, balanced resuscitation, initiating massive transfusion protocols, viscoelastic monitoring–guided

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resuscitation, and the use of whole blood and tranexamic acid in children.

Crystalloid

Until recently, the Advanced Trauma Life Support (ATLS) guidelines recommended the use of two 20-mL/kg crystalloid boluses for children in hemorrhagic shock prior to initiation of blood product transfusion (subcommittee, American College of Surgeons' Committee on, and International 2013). However, data from basic science and adult studies have shown that the use of crystalloid in trauma resuscitation may be harmful, and strategies that limit crystalloid volumes result in beneficial outcomes for both adults and children [9, 41, 56–58, 64, 67]. For example, laboratory data found high-volume crystalloid administration is associated with coagulopathy and hypothermia [58, 67]. One proposed deleterious mechanism is the dilutional effect of crystalloid, diminishing the blood's oxygen carrying capacity, and exacerbating TIC by interfering with clotting capabilities [41]. As a result, in adults, limited use of crystalloid and early use of blood products in trauma resuscitation is now the standard of care.

The data in children are concordant with adult studies in showing deleterious effects of crystalloid in trauma resuscitation. Two retrospective studies found upfront use of crystalloid delays blood product resuscitation and leads to volume overload [56, 64]. Schauer et al. found that combat-injured children who received high volumes of crystalloid had longer ventilator days and intensive care unit (ICU) durations [64]. Polites et al. first described a retrospective cohort of injured children with shock in whom increasing volumes of crystalloid were associated with increased duration of hospital stay [57]. This same group then conducted a multicentered prospective observational study in children with elevated prehospital shock scores and found increased crystalloid use was significantly associated with prolonged mechanical ventilation, ICU, and hospital length of stay (all $p < 0.05$). Additional crystalloid boluses were associated with increased need for blood transfusions, and time to blood transfusion was associated with extended ventilator duration (OR 1.1, $p = 0.04$) [56]. Further, the use of large volumes of crystalloid was found to negate any potential beneficial effects of early product resuscitation, suggesting that both crystalloid-sparing strategy as well as an early product strategy are important components in optimizing resuscitation practice [56].

Overall, current literature suggests children in hemorrhagic shock benefit from fewer crystalloid boluses to prevent the deleterious effects of dilution and volume overload. While these data suggest that children would benefit from avoiding high volume crystalloid resuscitation, better tools are needed to identify which injured children benefit most from early blood product transfusion. Current recommendations advise earlier utilization of blood products if significant resuscitation is required [75]; specifically, if crystalloid is given at all, it should be limited to one bolus, and if the child does not respond, they should subsequently receive blood products.

Massive Transfusion and Massive Transfusion Protocols

Injured patients can have substantial blood loss prior to hospital presentation, which can be exacerbated by trauma-induced coagulopathy. Both life-threatening hemorrhage and massive transfusion are uncommon in children. A National Trauma Database study found only 0.04% of injured pediatric patient receive massive transfusion (MT) [69]. However, the mortality rate is extraordinarily high for children who receive MT at 30–50%, so it is essential to rapidly identify children who would benefit from MT in order to intervene and guide management [37, 38, 69]. Massive transfusion protocols (MTP) were developed to facilitate the rapid delivery of multiple blood products, while alerting blood banks for the potential need of additional products, thus streamlining the delivery of large volumes of blood products. The risks associated with MT are related to receiving large volumes of blood product, and include hyperkalemia, hypocalcemia, coagulopathy, hypothermia, Rh incompatibility, and transfusion reactions [50]. Despite this, adult studies have shown that MTPs decrease coagulopathy, morbidity, and mortality primarily by rapidly delivering balanced ratios of blood products [10, 25]. Adult data has shown increased mortality when the initiation of MT is delayed [28, 40, 65].

Defining Massive Transfusion

In children, research on MT has historically been limited due to varying definitions of MT, MTP activation criteria, and differing components of MTPs. One survey of pediatric hospitals in 2014 found MTPs were most commonly activated due to physician discretion (89% of survey respondents) and not based on objective data or scoring systems [27]. In 2015, Neff et al. defined massive transfusion as 40 mL/kg of blood products in 24-h in combat-injured children. This volume represents approximately half of the circulating blood volume in most children and was found to be associated with increased 24-h mortality (OR 2.5, $p = 0.007$) and in-hospital mortality (OR 2.58, $p < 0.001$) [45]. Using 40 mL/kg within 24 h as a MT threshold is limited in clinical applicability, however, as it is retrospective in nature, relies on a relatively long time interval, and is subject to survivor bias as preventable deaths in hemorrhaging patients may occur prior to

reaching this massive transfusion threshold. Rosenfeld et al. used the Pediatric Trauma Quality Improvement Project (TQIP) database to identify a shorter time interval. Their massive transfusion threshold was defined as 37 mL/kg of blood products over 4 h, which was associated with a need for hemorrhage control procedures (OR = 8.6, $p < 0.01$) and early mortality (OR = 4.24, $p < 0.01$) in a civilian pediatric trauma cohort [60]. This shorter time interval allows for earlier activation of MTP and can act as a prognostic indicator for immediate death and need for operative intervention.

Activating Massive Transfusion Protocols

Accurate identification of children who will need massive transfusion is an area of active research. Multiple rapid scoring systems have been evaluated in the adult literature to predict the need for a massive transfusion protocol [49, 59, 68], notably, these tools have demonstrated poor performance in the pediatric population [1]. One proposed clinical tool that can guide providers in activating MTPs in injured children is the ABCD score. The ABCD score is based on the adult assessment of blood consumption score (ABC score), which gives one point for penetrating mechanism, positive focused abdominal sonography for trauma (FAST), systolic blood pressure < 90, and heart rate > 120. A score > 1 is used as a trigger to activate MTPs [49]. Due to low sensitivities when translating the ABC score to children [1], the ABCD score was developed. The ABCD score includes penetrating mechanism, positive FAST, age-adjusted shock index (SIPA), base deficit (> − 8.8), and lactate (> 3.5). Phillips et al. found an ABCD score > 2 was 77.4% sensitive and 78.8% specific at predicting the need for MT in children [54], though this requires laboratory values that may not be available at the time of patient presentation and requires further external validation.

Another metric has recently been described in children, called the critical administration threshold (CAT). Adult data described CAT as receipt of > 2 units of RBCs over 1 h. CAT + adult trauma patients have fourfold higher odds of death, and CAT positivity was predictive of mortality in blunt trauma. Additionally, subsequent CAT + episodes were associated with increased odds of mortality [62]. Morgan et al. defined the pediatric CAT as > 20 mL/kg of total blood products within 1 h. Pediatric CAT positivity was associated with increased in-hospital mortality, need for surgical intervention, and additional bleeding episodes (Morgan 2022). The CAT may offer an early and objective way to trigger the initiation of MTPs by identifying patients at a high risk of additional bleeding episodes, morbidity, and mortality, though has yet to be validated in other pediatric trauma cohorts.

Impact and Development of Massive Transfusion Protocols

Massive transfusion protocols were developed to guide resuscitation, facilitate communication and logistical support, and permit expeditious delivery of specific ratios of blood products to prevent coagulopathy before its onset. A single-site prospective study on the implementation of a pediatric trauma MTP showed a fourfold decrease in time to administration of FFP (95% CI 35–70 min, $p < 0.0001$) and improvement in delivery of balanced resuscitation compared to pre-MTP patients (FFP:PRBC 1:1.8 vs 1:3.6, $p = 0.002$) [23].

Massive transfusion protocols should be developed with a multidisciplinary team and ensure blood products can be rapidly activated and delivered throughout the hospital. In comparison to adults, pediatric MTPs should include weight- or age-based categories due to differences in blood product transfusion volumes. The composition of MTPs may vary between institutions due to differing blood product availabilities, so it is essential to work closely with the blood bank. Limiting delays in transfusing plasma and platelets is essential to achieve efficient and balanced blood product resuscitation in children. Future multicenter, prospective studies assessing the epidemiology of MTP activation, therapies most utilized, and outcomes after MTP activation are needed to determine the most effective MTPs for injured pediatric patients. Examples of existing pediatric MTPs are provided in Fig. 1.

Balanced Resuscitation

Balanced resuscitation, defined as high ratio of PRBC:FFP:platelets, is now the standard of care for patients in hemorrhagic shock in many adult trauma centers. Damage control resuscitation utilizes balanced resuscitation with ratios approximating whole blood to prevent and immediately correct TIC, restore intravascular volume, preserve oxygen-carrying capacity, and repair the endothelium. Bleeding patients lose whole blood, therefore replacing a patient's blood volume with higher ratios of blood products approximating whole blood has been shown to improve outcomes in adults [3, 20, 25, 26, 29, 70]. Additionally, transfusion of unbalanced blood products has the potential to exacerbate coagulopathy in critically ill patients, especially during massive transfusion events. Two landmark adult studies, the PROPPR trial and PROMMTT study, found improved early survival, earlier hemostasis, and decreased mortality from exsanguination in patients who received balanced resuscitation [24, 25].

In children, early single-site, retrospective studies on balanced resuscitation in pediatric patients showed mixed

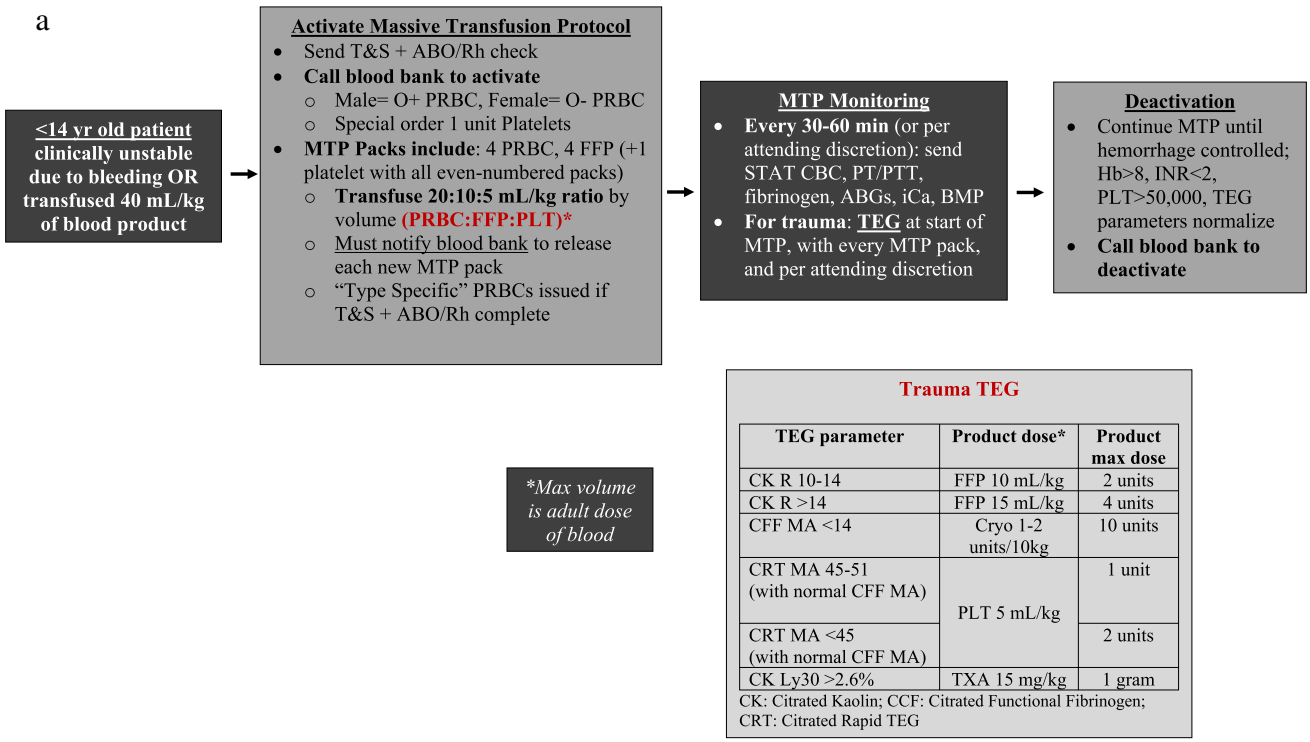

Fig. 1 Massive transfusion protocols from three children's hospitals. These figures show differing protocols for activating, administering, and monitoring massive transfusion protocols (MTPs) in injured children. **a** One institution's algorithm for MTP activation for children < 14 years old, including thromboelastography-guided resuscitation for injured children. **b** MTP activation and conventional coagulation test-guided resuscitation for children. **c** MTP and thromboelastography-guided resuscitation for injured children utilizing upfront whole blood. T&S: type and screen; PRBC: packed red blood cell; FFP: fresh frozen plasma, PLT: platelet; MTP: massive transfusion protocol; CBC: complete blood count; PT: prothrombin time; PTT: partial thromboplastin time; ABG: arterial blood gas; iCa: ionized calcium; BMP: basic metabolic panel; TEG: thromboelastography; Hb: hemoglobin; INR: international normalized ratio; Cryo: cryoprecipitate; TXA: tranexamic acid; MD: doctor; TM: Transfusion Medicine; ASAP: as soon as possible; lytes: electrolytes; Mg: magnesium; K: potassium; PRN: as needed; rTEG: rapid TEG; LDH: lactate dehydrogenase; ED: emergency department; OR: operating room

outcomes [6, 48]. However, more recent literature has shown balanced resuscitation is associated with improved survival in injured children [5, 12, 47]. Butler et al. evaluated the effect of blood component ratios on 24-h mortality rates in injured children receiving massive transfusion in the pediatric TQIP database. In a cohort of 583 injured children < 15 years old, high FFP:PRBC ratios (≥ 1:1), and medium FFP:PRBC ratios (≥ 1:2 and < 1:1) had a 51% absolute risk reduction (ARR, 95% CI: 0.27–0.87, $p = 0.02$) and 40% ARR (95% CI 0.39–0.92, $p = 0.02$) in mortality at 24 h, respectively, compared to the low ratio group (< 1:2). This mortality benefit remained even when excluding patients who were transferred or had severe TBI [5]. Additionally, a retrospective, multisite study of pediatric trauma centers found children who received massive transfusion (> 20 mL/kg of RBCs) had three times increased odds of mortality per unit increase over a 1:1 PRBC:FFP ratio (OR = 3.0, 95% CI 1.1–8.57, $p = 0.03$) [47].

In a recently published multicenter, prospective observational trial of traumatically injured children, the massive transfusion epidemiology and outcomes in children (MATIC) study, Spinella et al. found high FFP:PRBC ratios (> 1:2) were associated with improved 6-h survival compared to low ratios (OR = 0.12, 95% CI: 0.03–0.52, $p = 0.004$). Increased plasma deficit (RBC mL/kg minus plasma mL/kg), another metric by which to assess the balance of resuscitation, was associated with mortality in this same cohort; each 10 mL/kg of plasma deficit was associated with 10% and 20% increased odds of 6- and 24-h mortality, respectively [71, 72]. Platelet:PRBC ratios were not associated with survival; however, in children with greater platelet deficits (RBC mL/kg minus platelet mL/kg), 24-h mortality was increased by 10% for every 10-mL/kg platelet deficit [71, 72]. While these studies suggest balanced resuscitation is associated with improved outcomes in injured children, additional multicenter,

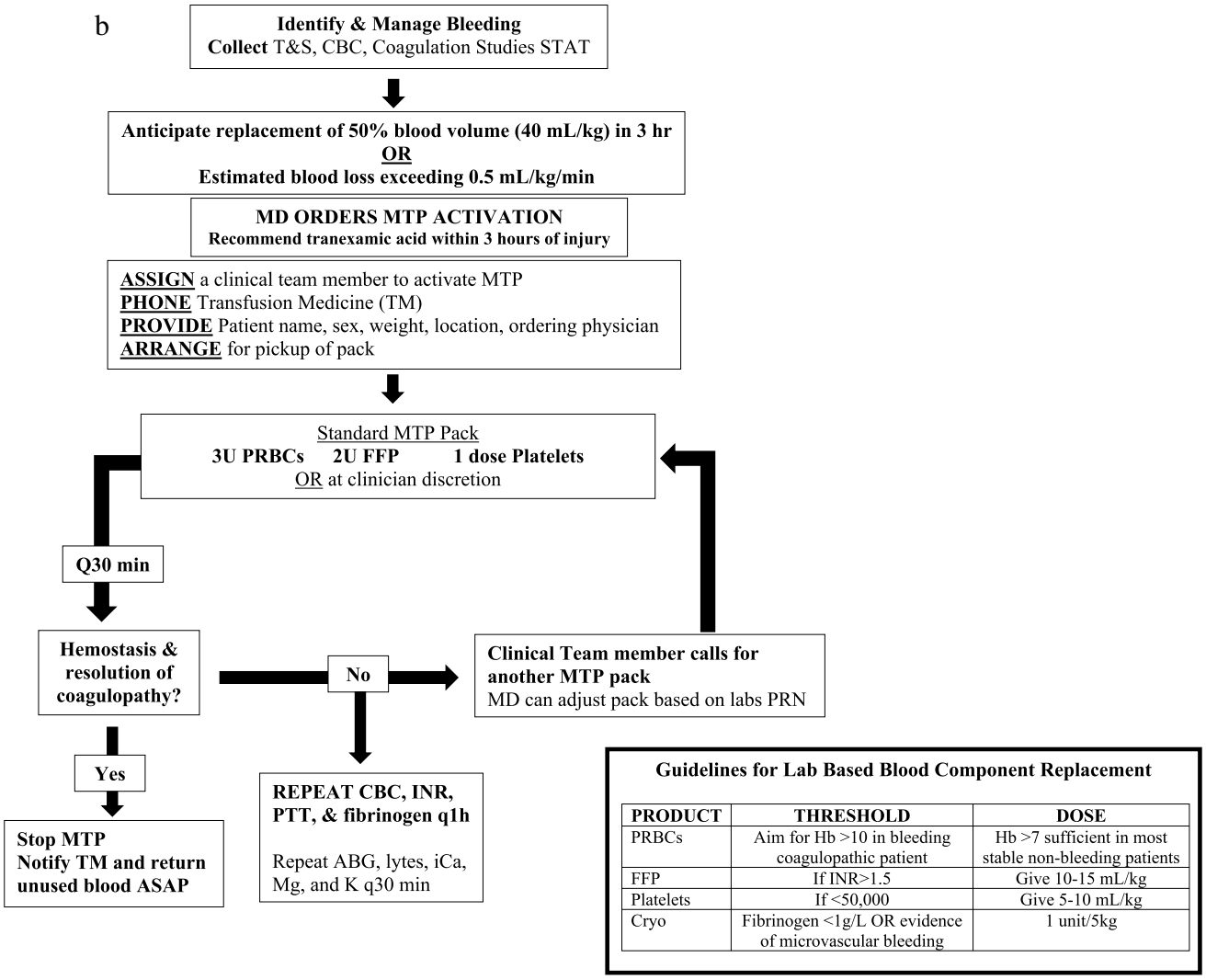

Fig. 1 (continued)

prospective studies are needed to determine the optimal blood product ratios to minimize morbidity and mortality in children.

TEG-Guided Resuscitation

There is a growing body of literature supporting the use of viscoelastic monitoring (VEM) in the assessment and treatment of trauma patients. VEM, which includes thromboelastography (TEG) and rotational thromboelastometry (ROTEM), use whole blood to measure various aspects of clot formation, stability, and degradation.

Results for these point of care assays are typically available more rapidly than conventional coagulation tests (CCT), including international normalized ratio (INR) and partial thromboplastin time (PTT), can be viewed in real time throughout the hospital using appropriate software platforms, and provide functional data on a patient's hemostatic status and coagulation profile, which can acutely guide resuscitation measures. Additionally, unlike VEM, traditional CCTs do not test fibrinolysis and hypercoagulability. Although data in children are less robust than in adult trauma cohorts, VEM-guided resuscitation in pediatric trauma shows promise by reporting coagulation values to aid in identification of critically injured patients who may benefit from goal-directed resuscitation and treatment of coagulopathy.

A survey of providers caring for injured children found 63% had access to VEM, but only 31% used it regularly despite literature reporting some benefits [61]. This may be attributable to limited pediatric-specific data, unfamiliarity with the interpretation of VEM, and lack of appropriate laboratory resources to

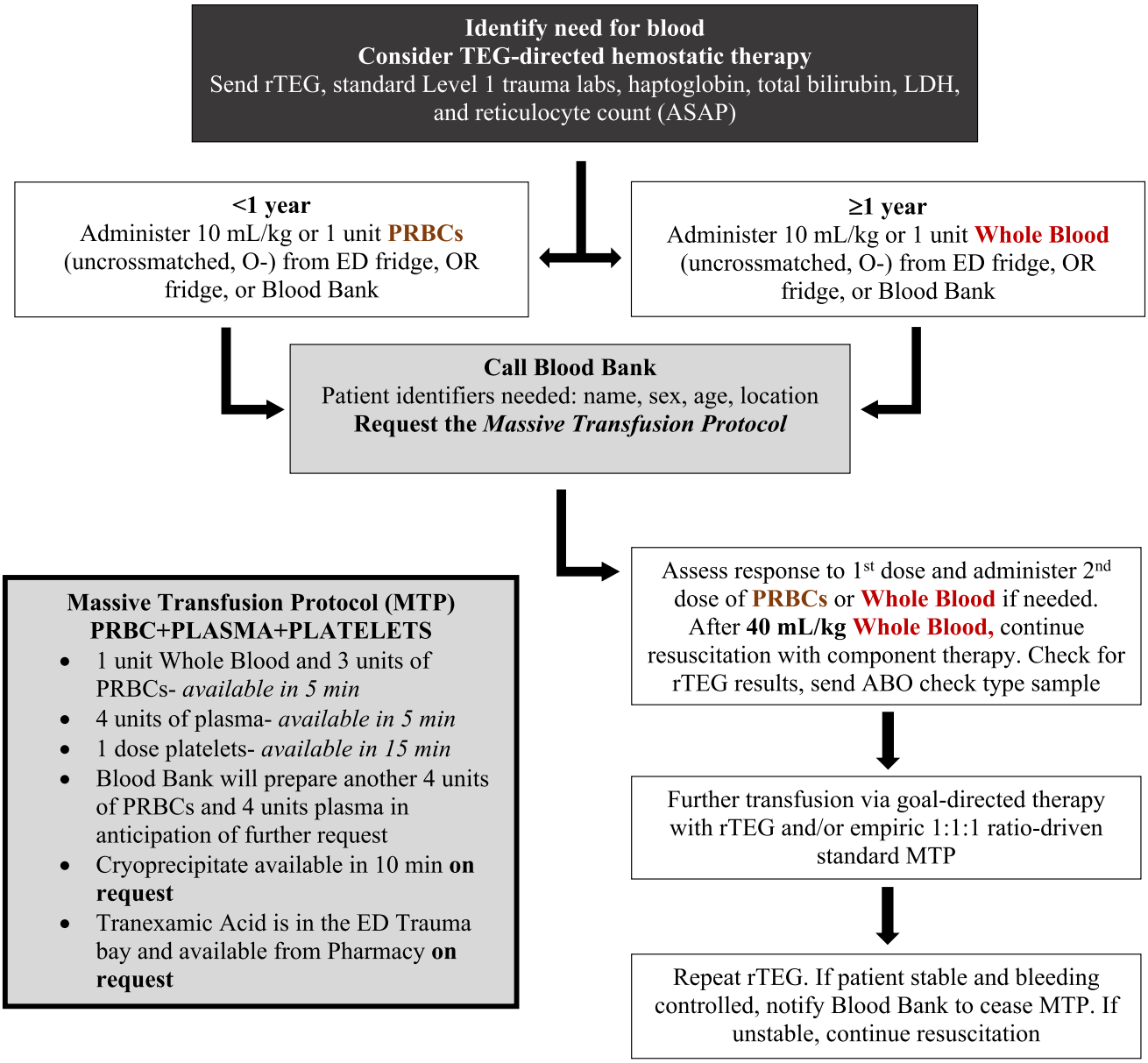

Fig. 1 (continued)

run the assays [63]. The existing pediatric trauma data on VEM-guided resuscitation is derived largely from retrospective and/or single-site studies. Vogel et al. found admission TEG correlated with CCTs and was predictive of the need for early blood product transfusion, early lifesaving interventions, and mortality [76]. Cunningham et al. showed coagulation dysregulation on ROTEM was associated with disability and mortality in injured children [11]. One multicenter, retrospective review on children < 15 years old who sustained blunt trauma found the use of ROTEM-guided resuscitation was associated with a significant reduction in the time to first coagulopathy treatment, less plasma transfusions in the first 24 h, and decreased hospital length of stay [15]. A 2016 Cochrane review on the use of VEM-directed resuscitation strategies in bleeding children and adults found a VEM-guided resuscitation strategy was associated with decreased mortality, need for blood products, and morbidity,however, a sizeable portion of the cohort was comprised of cardiac surgery patients (Wikkelso et al. 2016). Additional data in pediatric trauma cohorts are needed to inform resuscitation guidelines. Figure 2 shows an example of one institution's TEG-guided resuscitation algorithm with recommended blood product volumes to administer based on TEG value abnormalities.

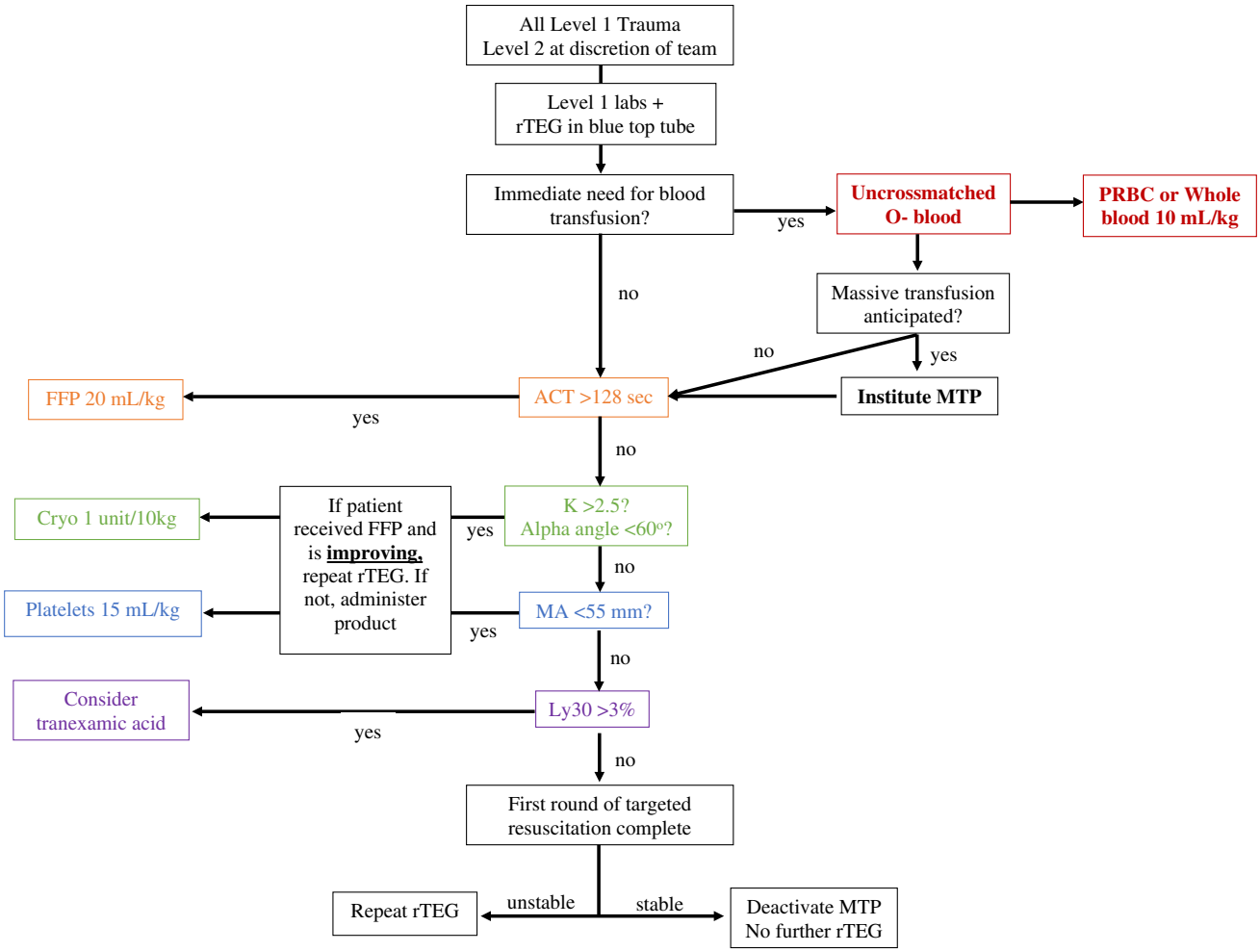

Fig. 2 Thromboelastography-guided resuscitation protocol. An algorithm for thromboelastography (TEG)-guided resuscitation for injured children. Level 1 trauma activations occur in the most severely injured patients. A rapid TEG (rTEG) is obtained on all level 1 and select level 2 trauma patients. If a transfusion is required, 10 mL/kg of uncrossmatched O negative blood is administered. If there is ongoing bleeding, the massive transfusion protocol (MTP) can be activated. Once rTEG results, blood products are administered based on rTEG value derangements shown in the figure. Additional rTEGs are obtained after the completion of each round of resuscitation; if there is ongoing evidence of clinical or lab-based coagulopathy, blood product resuscitation continues. If the child stabilizes, the MTP is deactivated and serial rTEGs are discontinued. rTEG: rapid thromboelastography, PRBC: packed red blood cell; MTP: massive transfusion protocol; FFP: fresh frozen plasma; Cryo: cryoprecipitate

Whole Blood

Balanced resuscitation with component therapy (CT; plasma, platelets, and RBCs) can be challenging to achieve in children due to limited intravenous access, blood product availability, and other logistic challenges. Low titer cold-stored group O whole blood (LTOWB) has been proposed as an alternative to component products. LTOWB is collected from male donors with low titers of anti-A and anti-B antibodies; it can be leukoreduced with or without an in-line platelet sparing filter. As it approaches expiration (14–35 days depending on local protocols), it can be reprocessed into a RBC unit. Compared to CT, LTOWB may have logistical advantages, increased potency compared to equal amounts of conventional components, and superior hemostatic capabilities [36, 78]. Multiple studies have reported that transfusion of LTOWB in adult and pediatric trauma patients is safe, with no transfusion reactions and no statistical differences in hemolytic markers between group O and non-group O recipients [22, 42]. For these reasons, there is renewed interest in utilizing cold-stored LTOWB as the initial resuscitative fluid in children with hemorrhagic shock.

In adults, use of LTOWB has been associated with improved survival and decreased blood product utilization [4, 66, 77]. In pediatric trauma patients, whole blood utilization has been associated with increased efficiency, decreased mortality, decreased blood product requirements, and improved coagulation profiles in pediatric trauma cohorts

[2, 33–35]. In a propensity-matched cohort of pediatric patients who received LTOWB compared to component therapy, Leeper et al. found the LTOWB group had faster time to resolution of base deficit, lower post-transfusion INR, and decreased plasma and platelet transfusions [34]. In a TQIP study, Anand et al. reported decreased 4- and 24-h blood product utilization for recipients of LTOWB compared to recipients of CT alone [2]. In a cohort of massively transfused injured children, receipt of LTOWB was associated with reduced 72-h (OR = 0.23, $p = 0.009$) and 28-day (OR = 0.41, $p = 0.02$) mortality [19].

The use of LTOWB in bleeding children remains relatively uncommon. A 2021 survey reported at least 7 trauma centers are using LTOWB in the resuscitation of injured children and 3 additional centers are imminently implementing a pediatric LTOWB program (Meshkin 2022, in press). There is some variability in eligibility for LTOWB transfusion and characteristics of the LTOWB product itself across centers; additional studies are needed to generate evidence-based guidelines and to compare the efficacy of LTOWB versus CT in injured children.

There is new interest in utilizing Rh + LTOWB in trauma patients since Rh-blood is scarce compared to the demand, which is further complicated by finding male donors who have low antibody titers. The primary concern in transfusing Rh incompatible blood in females of child-bearing potential is the development of hemolytic disease of the fetus and newborn (HDFN) in future pregnancies. Yazer calculated the modern-day probability of severe HDFN affecting future pregnancy following transfusion of Rh + LTOWB to Rh-females of childbearing potential is low (0.3–6%) [79]. The decision to utilize Rh + blood products in Rh type unknown FCPs must balance the benefit of blood transfusion early in the resuscitation period in order to improve a girl's chances of survival, versus the risk of HDFN from occurring in future pregnancies if she survives the trauma. Studies are underway to assess the implications of increased Rh + product use, patient and parental willingness to accept emergent Rh incompatible blood transfusion, and the means of increasing LTOWB supply available by increasing anti-A and anti-B titer thresholds.

Tranexamic Acid

Hemostatic adjuncts, namely tranexamic acid (TXA), are standard of care in adults in light of literature showing mortality benefits in trauma and obstetric cohorts. As with other resuscitation topics, there is little data to guide clinicians regarding the optimal use of hemostatic adjuncts in injured children. TXA is a pharmacologic adjunct that prevents fibrinolysis by inhibiting plasminogen activation and is used in the management of life-threatening hemorrhage in severely injured adults. Multiple adult studies, including CRASH-2, CRASH-3, and MATTERS studies, have shown the use of TXA is associated with improved survival [8],collaborators 2019; [44]. TXA was initially used in pediatric surgical patients, i.e., cardiac surgery, and was associated with decreased intra-operative bleeding and transfusion requirements with no adverse side effects [53]. Eckert et al. described the use of TXA in severely combat-injured children [16]. After adjusting for age, injury type, injury-severity scale, vital signs, initial hematocrit, and base deficit, receipt of TXA was associated with 73% decreased odds of mortality ($p = 0.03$) with no differences in thromboembolic complications or seizures. A propensity-matched analysis found no mortality differences, but children who received TXA had improved neurologic status at discharge and decreased ventilator dependence [16]. A larger study utilizing the Department of Defense Trauma Registry found massively transfused (≥40 mL/kg) children < 18 years who received TXA had significantly reduced odds of in-hospital mortality (OR = 0.35, 95% CI 0.123–0.995, p 0.049) after adjusting for age, sex, head abbreviated injury score, base deficit, mechanism of injury, and FFP/PRBC ratio [21].

Translating these studies to civilian populations is suboptimal, as a substantial majority of children in this study experienced blast or penetrating trauma, out of proportion to what is seen in a typical civilian pediatric cohort. In a secondary analysis of the aforementioned MATIC study, Spinella et al. reported that administration of antifibrinolytic agents was independently associated with improved 6- and 24-h survival in civilian children with life-threatening hemorrhage [71, 72]. This study had a mixed population of operative, medical, and traumatic hemorrhage,however, it was the first multicenter prospective analysis to show an early mortality benefit in bleeding children. Other civilian pediatric literature has failed to show this mortality benefit [39, 74], and one study demonstrated increased risk of seizures in injured children who receive TXA [39]. Clinical trials are needed to determine safety, efficacy, and indications for the use of TXA in injured children.

Conclusions

Rapid identification of patients at risk of decompensation from traumatic hemorrhage is essential in order to provide early and aggressive resuscitation. This can be particularly challenging in children due to their superior compensatory mechanisms. Although new thresholds and scoring systems have been developed to identify these children (i.e., CAT and ABCD score), prospective and multisite studies are still needed prior to universal application. Current literature in children supports limiting crystalloid administration, with consideration of using upfront blood products

for resuscitation in pediatric traumatic hemorrhage. Both balanced ratio and VEM-guided resuscitation strategies are associated with improved clinical outcomes in pediatric trauma patients; however, the data is limited. Use of whole blood has been shown to be safe and associated with improved outcomes in injured children and provides a logistical means of achieving balanced resuscitation. Tranexamic acid appears to be a safe and effective hemostatic adjunct in injured bleeding children, though further research is needed to confirm these findings.

Pediatric trauma resuscitation practices frequently rely on adult data. Existing pediatric-specific literature is often limited and under-powered; therefore, efforts to accumulate high quality data in support of defining optimal hemostatic resuscitation practices in children should be prioritized.

Declarations

Conflict of interest The authors declare no competing interests.

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• Of importance
•• Of major importance

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