Fifteen-minute consultation: a guide to paediatric major haemorrhage

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ABSTRACT

Major trauma is a principal cause of morbidity and mortality in children. Severe haemorrhage is the second-leading cause of death in paediatric trauma, preceded by traumatic brain injury. Major haemorrhage protocols (MHPs), also known as 'code red' and 'massive transfusion protocols', are used to make large volumes of blood products rapidly available. Most recommendations for paediatric MHPs are extrapolated from adult data because of a lack of large, high-quality, prospective paediatric studies. However, applying adult data in a paediatric context requires caution due to differences in injury mechanisms and physiological responses between adults and children. Since major haemorrhage is a high-acuity low-occurrence event, MHP requires effective training, collaboration and communication among a large multidisciplinary team.

In this 15-minute consultation, we provide an evidence-based synthesis of the management principles of paediatric major haemorrhage.

CASE

A 6-year-old boy arrives in the emergency department (ED) after being hit by a car. On the primary survey,[1] he maintains his airway and has bilateral breath sounds. However, he is tachycardic with a heart rate of 142 and hypotensive with blood pressure of 78/42 mm Hg. There is bruising to the abdomen. As the team works to establish intravenous access with two large-gauge cannulae, the trauma team leader announces, "This child may have life-threatening haemorrhage. Activate the major haemorrhage protocol."

DEFINITION OF PAEDIATRIC MAJOR HAEMORRHAGE

There are multiple definitions of paediatric major haemorrhage including: blood loss of 40 mL/kg over 24 hours; transfusion of ≥50% of total blood volume in 3 hours; transfusion of 100% of total blood volume in 24 hours; and bleeding with clinical signs of hypovolaemic shock that is unlikely to be controlled.[2] At this time, no single definition has been agreed upon. This variation highlights one of the main difficulties in comparing data across multiple research trials addressing this topic. Many of these definitions include measurement of blood volume lost or transfused at hour-long time intervals, limiting their use in the acute setting of the ED.

THE LETHAL DIAMOND

Severe traumatic haemorrhage can lead to trauma-induced coagulopathy (TIC). In addition to replacing lost blood volume in traumatic haemorrhage, care must be taken to avoid other complications. 'The lethal triad' of coagulopathy, hypothermia and acidosis is well described, but the potential significance of hypocalcaemia has led many to rename it as 'the lethal diamond' or 'diamond of death'[3] (figure 1 and figure 2).

BLOOD PRODUCT RATIOS

One area of debate is the optimal ratio of plasma (typically fresh frozen plasma or FFP) to platelets and packed red blood cells (pRBCs). High ratios, also called balanced transfusion ratios (≤1:1:2 ratio of one FFP:one platelets:two or fewer pRBCs), compared with low or unbalanced ratios (>1:1:2 ratio of one FFP:one platelets:more than two pRBCs), have been proposed to mitigate against TIC.[4] However, there is no conclusive evidence that a high versus a low ratio improves mortality. The PROPPR trial, a large multicentre randomised trial in adult trauma patients, did find a significant reduction in deaths due to haemorrhage at 24 hours when high ratios (1:1:1)

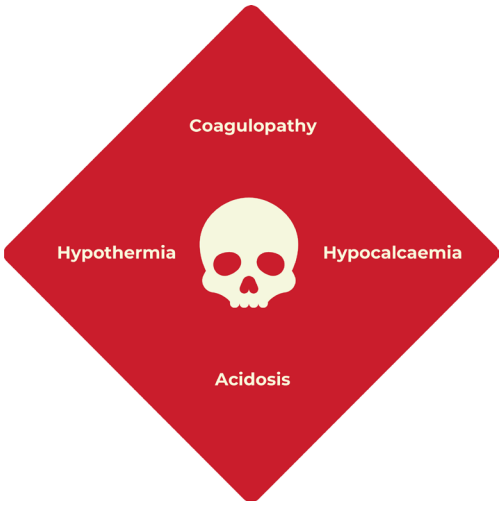

Figure 1 The lethal diamond of acidosis, coagulopathy, hypocalcaemia and hypothermia.

were given, though overall mortality was unaffected. Based on this trial, most adult guidelines recommend 1:1:1 ratios of FFP:platelets:pRBCs, but there is practice variability worldwide and among institutions.[5]

Results from paediatric studies assessing blood component ratios have been mixed. Currently, the optimal ratios for FFP:pRBCs and platelets:pRBCs are not known. A recent paediatric systematic review did not identify a mortality benefit favouring a high or low ratio,[6] though heterogeneity between trials and reliance on small retrospective studies limit confidence in these results.

In the absence of strong evidence favouring one approach, many paediatric MHPs mirror adult protocols and advocate for a 1:1:1 ratio of FFP:platelets:pRBCs.[7]

This can be difficult to achieve in practice as pRBCs are usually readily available while FFP requires time to thaw. As such, the actual ratios administered can end up being relatively low, with more pRBC relative to FFP and platelets. To address this and other challenges with infusing multiple individual blood components, there is debate regarding the merits of using a whole blood transfusion approach.[8]

CASE

The blood bank is notified, and a porter assists in the timely delivery of blood products to the ED. The patient receives the first unit of pRBCs. After this transfusion, his heart rate is 132 and his blood pressure is 70/35 mm Hg. His Glasgow Coma Scale is 13, respiratory rate is 25, SpO_2 97% in 15 L/min oxygen via a non-rebreather mask and temperature is 37°C. Clinical examination reveals bruising in the right upper quadrant, and there is clinical suspicion of a liver laceration. Additional blood products are being prepared. A trainee asks if there are any additional adjunctive therapies to consider.

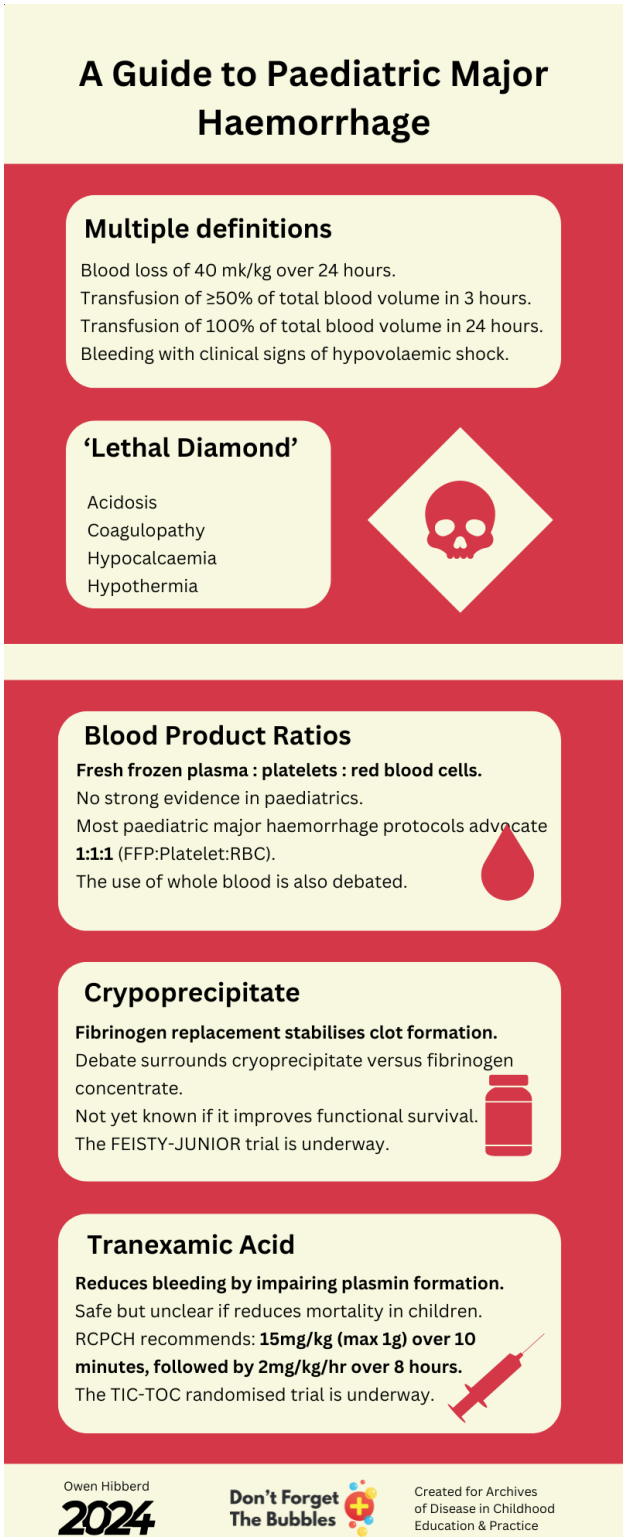

Figure 2 Infographic.

TRANEXAMIC ACID

Tranexamic acid (TXA) is an antifibrinolytic agent that stops bleeding by impairing plasmin formation. It has been shown to reduce transfusion

Table 1 Major haemorrhage protocol (MHP) team

Role/competency	Objective
Team leader	Activate the MHP, supervise entire process
Resuscitation team (cABCDE)	Run the resuscitation simultaneously
Communication lead	Perform all calls
Transfusion nurse	Prepare rapid transfuser, monitor and record blood products used
Medication nurse	Administer MHP adjuncts (eg, TXA, calcium)
Porter	Transport samples to the blood bank, bring blood products to the ED, return unused blood products to the blood bank
Haematologist on call	Optimise blood products used during MHP
Blood bank technicians	Organise blood products and how they are distributed
Scribe	Keep track of all medications given, procedures performed and document communication
Family support	Inform family about the progress

ED, emergency department; TXA, tranexamic acid.

requirements in several conditions. While studied in adults for managing major haemorrhage, its use and dosage in children remain unknown, resulting in variable practices worldwide.

Evidence from adult studies suggests that TXA is safe. The CRASH-2 trial[9] showed a 30% reduction in major haemorrhage-related mortality in severely injured adults who received TXA within 3 hours of injury. This was further supported by the PATCH trial,[10] which highlighted the potential of prehospital TXA in lowering early haemorrhage-induced mortality, although neurological outcomes at 6 months were not improved. The CRASH-3 trial[11] illustrated TXA's safety in traumatic brain injury and reduction of associated fatalities in mild to moderate head-related injuries if administered within 3 hours. However, it had no impact on all-cause mortality.

A comprehensive 2022 systematic review and meta-analysis[12] of 14 paediatric studies showed that TXA is also safe in children, with no increased risk of thromboembolic events. However, it concluded that although evidence showed improved outcomes with TXA in military combat settings, it did not improve survival in paediatric trauma in civilian settings. Despite this, TXA continues to be used in major paediatric trauma cases, likely due to its good safety profile. The TIC-TOC trial (https://tictoctrial.org/), a multicentre randomised controlled trial randomising traumatically injured children to different doses of TXA compared with placebo, is currently recruiting across the American Pediatric Emergency Care Applied Research Network, and results are anticipated.

The Royal College of Paediatrics and Child Health recommends a bolus of 15 mg/kg (maximum 1 g) TXA via a 10-minute slow infusion, followed by a 2 mg/kg/hour infusion for 8 hours. However, the routine use of TXA in paediatric trauma varies worldwide.

Table 2 Example of checklist for managing major paediatric haemorrhage

Checklist for managing major paediatric haemorrhage	
Action	**Time completed**
Handover	
Primary survey (cABCDE)	
Application of haemostatic dressings or limb tourniquets	
Vascular access (×2), bair hugger/other temperature control measures	
Plan for definitive haemorrhage control (surgical or interventional radiology)	
Warmed packed red cells	
Warmed fresh frozen plasma	
Platelets	
Adjuncts (eg, tranexamic acid, warmed cryoprecipitate, calcium chloride)	

CRYOPRECIPITATE

Fibrinogen, a precursor to fibrin that stabilises clot formation, becomes depleted due to consumption, breakdown and dilution.[4] Although many centres use cryoprecipitate transfusions for fibrinogen replacement, they are often administered late in the resuscitation process. The Australian FEISTY multicentre randomised controlled trial[13] compared fibrinogen concentrate with cryoprecipitate and showed that in severely injured, hypofibrinogenaemic patients, fibrinogen concentrate may be administered faster than cryoprecipitate. The Cryostat-2 multicentre UK randomised controlled trial[14] showed no reduction in 28-day mortality in adult patients who received early high-dose cryoprecipitate.

It is not known whether fibrinogen replacement in the setting of TIC (whether with cryoprecipitate or fibrinogen concentrate) improves functional survival in adults or children. Currently, the first paediatric randomised controlled trial comparing fibrinogen concentrate and cryoprecipitate, FEISTY-JUNIOR Study (https://www.feisty.org.au/feisty-junior/), is underway.

VISCOELASTIC TESTING

Some trauma centres have the ability to perform viscoelastic testing, typically thromboelastography or rotational thromboelastometry. These tests may help guide targeted therapy and interventions in addressing coagulopathy. However, the ITACTIC trial conducted in adults compared this testing with

conventional coagulopathy testing and noted no difference in patient outcomes.[15] The usefulness of this testing is limited given that it is not available at all institutions or results may not be available in a timely manner. Further research is required.

CASE

As blood products are administered and the operating room is being prepared, the team notices that the boy's temperature has dropped to 35°C.

PREVENTING HYPOTHERMIA

Major haemorrhage can lead to hypovolaemic shock, placing patients at significant risk of hypothermia. Hypothermia is further exacerbated by environmental factors, infusion of unwarmed fluids and as a side effect of anaesthesia.[16] Its role as an independent risk factor for worsening coagulopathy, higher transfusion requirements and mortality is well established in adult trauma patients. Although evidence in paediatric trauma patients remains limited, an increase in mortality associated with hypothermia has been consistently demonstrated.[16]

Patients' temperatures should be carefully monitored so that hypothermia can be quickly addressed. There are many methods of warming. Active external rewarming includes removing cold, wet clothing, warming mattresses or radiant heaters. Active internal warming entails delivering warmed intravenous solutions using either a rapid infuser (eg, Belmont Rapid Infuser RI-2), or fluid warmer, or by using the three-way stopcock method[17] and ventilating with warmed humidified gases.[18] However, paediatric data are limited and further studies are needed to best define temperature targets and the optimal method of rapid transfusion.

CASE

After the boy receives pRBCs, his laboratory results return and demonstrate an ionised calcium (iCa) of 0.7 mmol/L.

CALCIUM

Calcium acts as an essential cofactor for many components of the coagulation cascade and platelet adhesion, and its depletion leads to progressive coagulopathy.[19] Low levels decrease vascular tone, myocardial function and contractility, worsening perfusion and acidosis.[19] iCa decreases in trauma both by acute blood loss, calcium-lactate binding, intracellular calcium influx in the context of ischaemic injury and chelation by citrate in the blood products used during resuscitation.[19]

A systematic review including 1213 major adult trauma patients demonstrated low iCa was associated with increased mortality, blood transfusion requirements and coagulopathy.[20] A few heterogeneous paediatric studies reflect similar findings.

Test your knowledge

1. What is included in the 'lethal diamond'?
   A. Coagulopathy, hyperthermia, alkalosis, hypocalcemia
   B. Coagulopathy, hypothermia, acidosis, hypocalcemia
   C. Coagulopathy, hypothermia, acidosis, hypercalcemia
   D. Coagulopathy, hyperthermia, acidosis, hypercalcemia
2. In paediatric traumatic massive haemorrhage, within how many hours from injury should tranexamic acid be given?
   A. 4-hours post injury
   B. 6-hours post injury
   C. 3-hours post injury
   D. 8-hours post injury
3. What is the target ionised calcium (iCa) level in trauma patients?
   A. >1,5 mmol/L
   B. >2 mmol/L
   C. >1 mmol/L
   D. >2.5 mmol/L
4. What ratio is currently recommended for blood products in paediatric major haemorrhage (FFP: platelets: pRBCs)?
   A. 1:2:1
   B. 1:1:2
   C. 2:1:1
   D. 1:1:1
5. Which of the following are active internal warming strategies?
   A. Removal of wet clothing
   B. Use of warm mattress
   C. Use of fluid warmer infuser
   D. Use of radiant heater

Answers to the quiz are at the end of the references.

Current practices recommend monitoring iCa and correcting hypocalcaemia to maintain an iCa >1 mmol/L.[5] This recommendation has predominantly evolved from adult data, highlighting a need to explore its incidence, trends and possible adverse outcomes in the paediatric population. A systematic review and meta-analysis addressing this question is currently underway.[21 22]

CASE

The boy is brought to the operating room for further care and admitted to the paediatric intensive care unit following surgery. The team convenes afterwards to debrief.

TRAINING

MHP is a high-acuity low-occurrence event, and training is essential to improving clinical outcomes.

Each MHP activation involves a multidisciplinary team (table 1).

Simulation studies show improved adherence to MHP, enhanced team communication and a reduction of cognitive load.[23] The use of checklists also increases adherence to protocol steps (table 2).

CONCLUSION

The early recognition and treatment of paediatric major haemorrhage significantly impacts a child's morbidity and mortality. There is currently no consensus definition for paediatric major haemorrhage. MHPs can be activated to deliver large volumes of blood and blood products but are resource-intensive and require the coordination of a multidisciplinary team.

Much of the evidence for the optimal ratio for balanced transfusion and adjunctive therapies is derived from adult studies, with more paediatric studies underway. Currently, many institutions use high ratios for balanced transfusion (1:1:1 of FFP:platelets:pRBCs). Care must be taken to avoid complications such as acidosis, coagulopathy, hypothermia and hypocalcaemia during resuscitation.

Clinical bottom line

- There is no consensus definition for paediatric major haemorrhage.
- Much of the evidence for paediatric major haemorrhage protocols (MHPs), balanced transfusion ratios and adjunctive therapies are derived from adult studies with paediatric studies underway.
- Currently, many paediatric MHPs favour a 1:1:1 ratio of fresh frozen plasma:platelets:packed red blood cells.
- Care must be taken to avoid the lethal diamond (coagulopathy, acidosis, hypothermia and hypocalcaemia) during resuscitation.
- MHPs are resource-intensive and require collaboration among a multidisciplinary team.

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Answers to the multiple-choice questions

1. B
'Lethal triad' of coagulopathy, hypothermia and acidosis is well described, but the potential significance of hypocalcaemia led many to rename it as the 'lethal diamond'.
2. **C**
In adult patients, tranexamic acid has been shown to be safe in major trauma and traumatic brain injury and associated with a reduction in mortality in mild to moderate head-related injuries if administered within three hours. Data is extrapolated to paediatric patients.
3. **C**
Current practices recommend monitoring iCa and correcting hypocalcaemia to maintain an iCa > 1mmol/l
4. **D**
In the absence of strong evidence favouring one approach, many paediatric major haemorrhage protocols mirror adult protocols and advocate for a 1:1:1 ratio of FFP: platelets: pRBCs
5. **C**
Active internal warming entails delivering warmed IV solutions and ventilating with warmed humidified gases

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