OXFORD

Revalidation FOR ANAESTHETISTS RCA Revalidation matrix Matrix reference 1B04, 2D02, 3D00

BJA Education, 16 (8): 269–275 (2016)

doi: 10.1093/bjaed/mkv051
Advance Access Publication Date: 15 November 2015

Paediatric massive transfusion

S Blain MBBS[1,*] and N Paterson MB ChB DA FFA FANZCA[2]

[1]Provisional Fellow, Royal Brisbane and Women's Hospital, PO Box 404, Brisbane, QLD 4006, Australia and [2]Consultant Anaesthetist, Royal Children's Hospital, Herston Road, Herston, Brisbane, QLD 4006, Australia

*To whom correspondence should be addressed. E-mail: stu.blain@gmail.com

Key points

- Defined by red blood cell transfusion of 50% of total blood volume (TBV) in 3 h, 100% in 24 h, or >10% of TBV per minute.
- Massive blood loss in the paediatric patient, often from blunt trauma, can be difficult to assess. Surgical bleeding is often anticipated and usually occurs in a monitored environment where blood loss can be assessed as it occurs.
- The underlying cause of haemorrhage and subsequent management has a profound effect on the body's ability to maintain haemostasis.
- Management requires assessment of the degree of blood loss and replacement of blood products to maintain volume and haemostasis. This may be assisted by the application of a 'massive transfusion protocol'.
- Point-of-care testing (thromboelastography, ROTEM) and the use of individual clotting factors may offer more timely and direct means of correcting coagulopathy from massive blood loss.

Defining paediatric massive transfusion

Diab and colleagues[1] suggested the following:

(i) Packed red blood cell (PRBC) transfusion of 50% of total blood volume (TBV) in 3 h,
(ii) PRBC transfusion of 100% TBV in 3 h,
(iii) PRBC transfusion of >10% of TBV min^{-1}.

Pathophysiology of massive blood loss and transfusion

Figure 1, adapted from Diab and colleagues,[1] identifies pathophysiological factors contributing to coagulopathy during massive transfusion. It identifies the changes that occur during trauma and surgery as a consequence of tissue injury, blood loss, and therapeutic interventions.

Trauma-induced coagulopathy is a multi-factorial process. Tissue damage results in the release of tissue factor and subsequent activation of the coagulation cascade. Hypoperfusion that occurs after massive blood loss causes increased expression of thrombomodulin in turn binding to thrombin and activating protein C. Activated protein C inhibits cofactors V and VIII and in excess also depletes plasminogen activator inhibitor-1 (PAI-1), reducing tissue plasminogen activator inhibition and accelerating the formation of plasmin and fibrinolysis. Similar pathophysiological changes can occur during major surgery with massive blood loss.[1]

Coagulopathy may also develop during massive transfusion. This occurs as a result of haemodilution from volume replacement and can be exacerbated by hypothermia and acidosis. The storage temperature of blood products at 1–6°C can contribute to hypothermia in patients requiring massive transfusion. For each 1°C decrease in temperature, coagulation factor activity decreases by 10%. Below 34°C, clotting times prolong, platelets pool within the spleen, and there is impaired adherence and aggregation. Significant hypocalcaemia (ionized calcium <0.6 mmol $litre^{-1}$), induced by blood product citrate binding to circulating serum calcium and acidosis (pH<7.3), reduces the activation of coagulation on platelet cell surfaces and disrupts haemostasis.[2]

Certain patient groups are more prone to massive blood loss. Neonates comprise a special at-risk group. The haemostatic system is incompletely developed at birth and matures throughout infancy. The concentration of procoagulant and anticoagulant

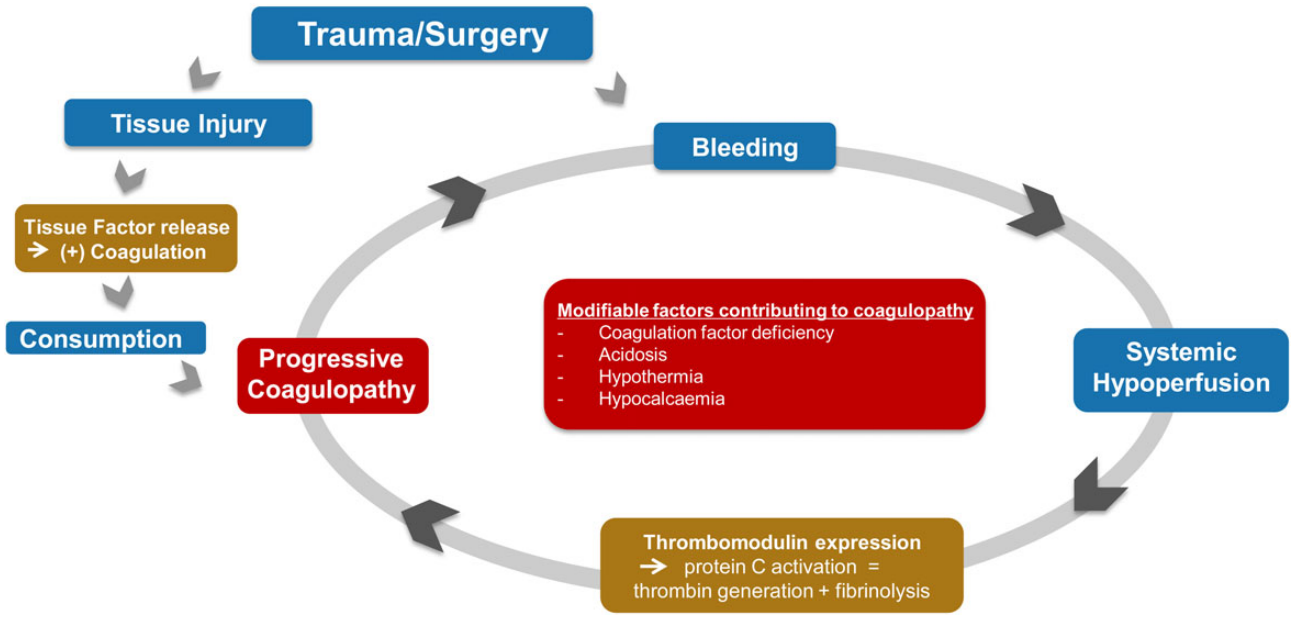

Fig 1 Pathophysiological factors contributing to coagulopathy during massive transfusion. (Modified from Fig. 1 of Diab and colleagues, with permission from *British Journal of Haematology*, John Wiley and Sons.)[1]

proteins is low and remains so until 6 months of age. Fibrinogen is qualitatively dysfunctional, existing in fetal form for 6–12 months after birth.[1] Consequently, the haemostatic changes during massive transfusion in this population are profound, often resulting in an increased bleeding risk. In addition, burns patients may have a consumptive coagulopathy with microangiopathic haemolysis, cardiac patients undergo the haematological insult induced by bypass, and patients in liver failure may have reduced levels of clotting factors and thrombocytopaenia.[1]

Management of massive transfusion

Assessment of blood loss

The principles of assessing paediatric massive blood loss are similar to adults. They rely on clinical signs, symptoms, monitoring, and investigations. As with adults, dyspnoea, altered mentation, hypotension, and reduced capillary refill can be used to assess haemodynamic state. However, paediatric patients have good physiological reserve, maintaining arterial pressure even after a loss of 25–40% of blood volume. Consequently, the clinical signs and symptoms of hypovolaemia may not be good predictors of early haemorrhage. A narrow pulse pressure may be a more sensitive sign of hypovolaemia than tachycardia or systolic hypotension. Lactic acidosis secondary to hypoperfusion and decreased urine output are additional indicators of hypovolaemia. Invasive monitoring in the form of intra-arterial and central venous pressure monitoring may be indicated if blood loss is assessed to be greater than one blood volume, further losses are expected, there is serious head injury, or there is major trauma of unknown severity. It may also assist the assessment of peripheral oxygenation via measurement of lactate and mixed venous oxygen saturation.

Assessment of blood loss in theatre can be difficult. Clinical signs are affected by anaesthesia and blood loss calculated by direct observation, collection in suction bottles, and weighing of swabs are inaccurate and impractical, often underestimating volume lost.[1] Despite difficulty in using clinical signs and symptoms to determine paediatric blood loss, transfusion requirements using volumes of crystalloid and blood products given to maintain vital parameters (including heart rate, arterial pressure, central venous pressure) can be used to help determine the degree of blood loss. Blood loss being approximated as one-third of crystalloid or an equivalent volume of colloid replacement required to maintain haemodynamic stability.[3] Of note, the estimated blood volume of a preterm infant is 90–100 ml kg^{-1}, a term infant <3 months 80–90 ml kg^{-1}, and a child >3 months 70 ml kg^{-1}.[1]

Blood volume replacement strategies

The management of massive transfusion requires that circulating blood volume is restored and blood components are given such that haemostasis is maintained or returned to normal. In uncontrolled haemorrhage, damage control or haemostatic resuscitation aims to minimize iatrogenic resuscitation injury, prevent worsening of shock and coagulopathy, and obtain definitive haemostasis, usually via surgical control. It differs from the traditional management of haemorrhagic shock by limiting crystalloid fluid resuscitation and by transfusing blood products empirically before coagulopathy is identified by testing. In the paediatric trauma setting, increased crystalloid volume replacement has been associated with increased transfusion requirements, coagulopathy (prolonged prothrombin times), and a tendency towards increased mortality and multi-organ failure rates.[4]

Permissive hypotension is a fluid management strategy, often used in adult trauma settings, that targets a suboptimal arterial pressure until definitive management of bleeding can be obtained. It aims to maintain end-organ perfusion while limiting crystalloid resuscitation, thereby limiting dilutional coagulopathy, clot disruption, and cellular dysfunction. Evidence for use in both the adult and paediatric population is limited. Given that children have a large physiological reserve and compensate for blood loss with minimal change in vital signs, it may not be an appropriate strategy in the paediatric population.

An important concept of haemostatic resuscitation is construction of a balanced transfusion strategy delivering red blood cells, fresh-frozen plasma (FFP), platelets, coagulation factors, and anti-fibrinolytics. Early administration of predefined balanced ratios of PRBC, FFP, and platelets has been associated with improvements in patient outcomes in adult trauma and non-trauma patients. Particularly those receiving higher ratios of FFP and platelets to PRBC than have been used in the past.[4] Evidence for the optimal product ratio, in both adult and paediatric patients, is yet to be determined. Despite this, many adult massive transfusion protocols suggest a PRBC:FFP:platelets ratio of 1:1:1 to best represent whole blood loss, with early consideration of fibrinogen replacement and use of tranexamic acid (TXA) in specific circumstances. Of note, research into lower PRBC:FFP ratios during massive transfusion in children is yet to indicate significant improvements in morbidity and mortality.[5] For this reason, and possibly due to difficulty in providing FFP quickly, most guidelines advocate replacement in a PRBC:FFP:platelet ratio of 2:1:1.

The composition of volume replacement during massive blood loss can vary depending on the clinical circumstance. In the trauma setting, patients can sustain coagulopathy from tissue factor released from damaged tissues and hypoperfusion, often requiring early replacement of fibrinogen and coagulation factors. In the surgical setting, preoperative tissue injury and volume depletion is less likely and patients often have invasive monitoring in a regulated theatre environment. Blood loss can often be assessed by monitored vital parameters, laboratory testing, and required fluid replacement. Red blood cell replacement is guided by transfusion thresholds and estimated blood loss. If bleeding is controlled, the introduction of PRBC can be guided by the use of a maximal allowable blood loss equation and clinical response to fluid therapy. An equation in common use is as follows:

$$\text{Maximal allowable blood loss} = \left(\frac{\text{Hb initial} - \text{Hb low}}{\text{Hb initial}}\right) \times \text{EBV}$$

where Hb initial is starting Hb and Hb low is acceptable threshold Hb below which red cell replacement should begin. Hb low should be determined with consideration of patient condition and clinical situation EBV is estimated blood volume.

For example, a 10-yr-old child that weighs 30 kg is undergoing surgery where significant blood loss is expected. Starting Hb is 13 g dl^{-1} and acceptable low Hb is deemed to be 7 g dl^{-1}. Estimated blood volume is 70 ml kg^{-1}×30 kg or 2100 ml.

$$\text{Allowable blood loss} = \frac{13 - 7}{13} \times 2100 \text{ or } 970 \text{ ml}$$

PRBC transfusion should therefore be considered after assessed loss of ~1 litre of blood.

Further administration of other blood products including platelets and cryoprecipitate can be guided by standard laboratory or point-of-care testing. If speed of blood loss precludes this, introduction of platelet therapy after one or two blood volumes loss and cryoprecipitate after three blood volumes loss has been described.[3]

Once bleeding has been controlled, volume restored and blood products administered, appropriate therapeutic targets after massive transfusion could include the following: Hb 80 g $litre^{-1}$, fibrinogen >1.0 g $litre^{-1}$, PT ratio <1.5, platelet count >75×10^9 $litre^{-1}$ (excluding traumatic head injury 100×10^9).

Table 1 Flow rates of i.v., intraosseous cannulas[6]

I.V. catheter	Maximum rate of flow with gravity (ml min^{-1})	Maximum rate of flow with pressure (ml min^{-1})
14 G 50 mm cannula	236.1	384.2
16 G 50 mm cannula	154.7	334.4
18 G 45 mm cannula	98.1	153.1
20 G 33 mm cannula	64.4	105.1
22 G 25 mm cannula	35.7	71.4
15 G 25 mm intraosseous needle (tibial)	68.2	204.6

Equipment during a massive transfusion

Administration of large volumes of blood products requires adequate vascular access. During paediatric trauma where massive haemorrhage is suspected, if no access is established after 90 s or two attempts, intraosseous access is appropriate. Table 1 indicates flow rates of i.v. and intraosseous cannulas of differing gauge and length.[6]

Products need to be warmed and the rate of transfusion will indicate which method of warming will be most suitable. Devices using countercurrent exchange (Level 1 fast flow H-1200; Smiths Medical, London, UK) and magnetic induction (FMS 2000; Belmont Instrument Corp., Billerica, MA, USA) should be used for patients requiring increased transfusion volumes (>100 ml min^{-1}). At moderate flow rates (<100 ml min^{-1}), there is significant heat loss after i.v. tubing leaves the warmer. If small volumes of transfusion are required directly warming blood via insulating i.v. tubing can be effective or utilizing an in-line warmer close to the infusion site (Buddy, Belmont Instrument Corp.).[7]

Blood salvage is used in the paediatric setting. Initially, when cell salvage was introduced into paediatric practice 'fixed volume bowls' of >300 ml volume were used, so that blood loss required needed to be >500 ml. However, advances in technology have allowed for the use of smaller bowls (down to 50 ml) and more recently 'continuous disc or centrifugal processing' allowing smaller volumes of blood to be processed faster.[7] Its use in elective or emergency procedures should be considered when anticipated blood loss is >20% of the patients estimated blood volume. Allogenic blood transfusion was significantly reduced in volume and frequency when used in craniofacial, major orthopaedic (acetabuloplasty and scoliosis correction), and complex cardiac surgery.[8] Cell savers have an additional use as they can wash PRBC before transfusion in cases where significant blood loss is expected. High levels of potassium and hydrogen ions after storage are washed out and the resulting hyperkalaemia and acidosis from rapid transfusion, particularly in smaller children, can be mitigated.

Complications of massive transfusions

Table 2 indicates complications and management suggestions after massive transfusions. Complications can be divided into transfusion reactions, immunological, metabolic, and miscellaneous. Along with the risks associated with single unit blood transfusions, patients receiving greater volumes of transfusion are more prone to complications, particularly those contributing to coagulopathy—hypocalcaemia, acidosis, and hypothermia.

Table 2 Complications and management suggestions after massive transfusions (modified from Table 1 in Diab and colleagues, with permission from *British Journal of Haematology*, John Wiley and Sons)[1]

Complication	Comments and management suggestions
Transfusion reactions	
Allergic	Range from urticarial to anaphylaxis. Consider steroids or diphenhydramine
Haemolytic transfusion reaction (acute, and delayed)	Consider giving O RBCs and AB plasma for emergency released blood products
Febrile non-haemolytic transfusion reaction	
Immununological complications	
Transfusion-related acute lung injury (TRALI)	
Transfusion-related immunomodulation (TRIM)	May be responsible for increased risk of bacterial infection
Transfusion-associated graft *vs* host disease (Ta-GVHD)	Irradiation of cellular blood products for patients at risk (neonates, immunosuppressed)
Metabolic complications	
Hypocalcaemia	Citrate overload from rapid transfusion, neonates and patients with liver disease are at higher risk
Hypomagnesaemia	Transfusion of large volumes of magnesium poor fluid and citrate overload
Hyperkalaemia	From haemolysis of RBC from storage, irradiation. Fresh RBCs (<5–10 days old, irradiated <24 h before transfusion or washing may decrease risk
Hypokalaemia	Owing to re-entry into transfused blood cells, stress hormones, metabolic alkalosis
Metabolic alkalosis	Citrate overload
Acidosis	Owing to hypoperfusion, citrate overload, liver dysfunction
Hypothermia	
Miscellaneous	
Coagulopathy	Refer to pathophysiology section
Transfusion-associated circulatory overload (TACO)	Differs from TRALI. May require oxygen and diuretics
Air embolism	Potentially fatal complication. Careful use of rapid infuser

Massive transfusion protocols

Owing to the multi-factorial nature of coagulopathy during trauma and surgery, massive transfusion protocols have been developed to guide resuscitation, facilitate communication and logistical support, and prevent coagulopathy before it occurs. By standardizing the empirical use of blood products, they facilitate appropriate blood product replacement during critical haemorrhage. In the adult population, the use of massive transfusion protocols has resulted in faster delivery of blood products, decreased rates of multi-organ failure, and improved 30 day survival.[9] The early initiation of multi-component therapy, facilitated by reduced delays in ordering and delivery, has the potential to prevent excessive use of crystalloid, correct and prevent coagulopathy, and minimize the complications of massive transfusion.[4] Massive transfusion protocols, particularly in paediatric trauma settings, are yet to identify a reduction in mortality and morbidity, but have been shown to reduce time to transfusion.[5]

Predicting who will require a massive transfusion and triggering a massive transfusion protocol can be difficult. In the adult population, several scoring systems exist to predict likelihood of requiring a massive transfusion. Variables, including INR (>1.5), systolic arterial pressure (<90 mm Hg), haemoglobin (<11 g dl^{-1}), base deficit (>6), FAST scan positive, heart rate (120 beats min^{-1}), temperature (<35.5°C), penetrating trauma, and or pelvic/long bone fractures, have been used to predict the need for massive transfusion.[10] No similar scoring systems exist in the paediatric population.

Triggering a massive transfusion protocol

- Clinical identification of patient at risk. Determined by mechanism of injury (trauma, head injury, pelvic/long bone fractures), surgery, vital parameters [reduced systolic pressure, hypothermia (35°C)].
- Transfusion requirements. As per previous definition of massive transfusion.
- Biochemical analysis. Evidence of acidosis (base deficit >6), coagulopathy (INR>1.5), reduced haemoglobin (Hb<7 g dl^{-1}).

It is important to note that a massive transfusion protocol is not a blood product prescription. It is a pathway used to define when to initiate the protocol, what blood products to immediately release, which tests to utilize, and to activate arrangements for getting the blood products to the patient quickly. While packs are supplied containing designated units of blood products, administration remains as directed by the treating clinician in accordance with patient weight and clinical response. Logistical considerations during massive transfusion include early notification of blood bank and consultation with haematology. Theatre staff should be delegated responsibility for blood product collection, storage, and documentation of usage. Products should not be exposed to room temperature for longer than 20 min and unused products should be returned when appropriate. Blood bank should be notified of deactivation of the MTP.

An example of a paediatric massive transfusion protocol is displayed in Figure 2.[11]

Recent developments

Point-of-care testing

Laboratory evaluation of the massively bleeding paediatric patient is challenging and conventional coagulation assays including prothrombin time (PT), partial thromboplastin time (PTT), platelet count, and fibrinogen levels are time-consuming. Specific information on clot formation and haemostatic abnormalities such as platelet dysfunction, hyperfibrinolysis, and factor XIII deficiency are not provided. The use of thromboelastometry (TEG) and rotational thromboelastometry (ROTEM) measures coagulation in real time at the patients' current temperature and observes the viscoelastic properties of whole blood from initiation of coagulation to fibrinolysis. Despite no evidence that TEG and ROTEM reduce the morbidity and mortality in massively transfused patients, they do reduce time for availability of test results. This may better direct the early use of individual blood products and reduce transfusion requirements.[1 12] Such point-of-care testing may be a useful adjunct to conventional testing for paediatric patients requiring massive transfusion.

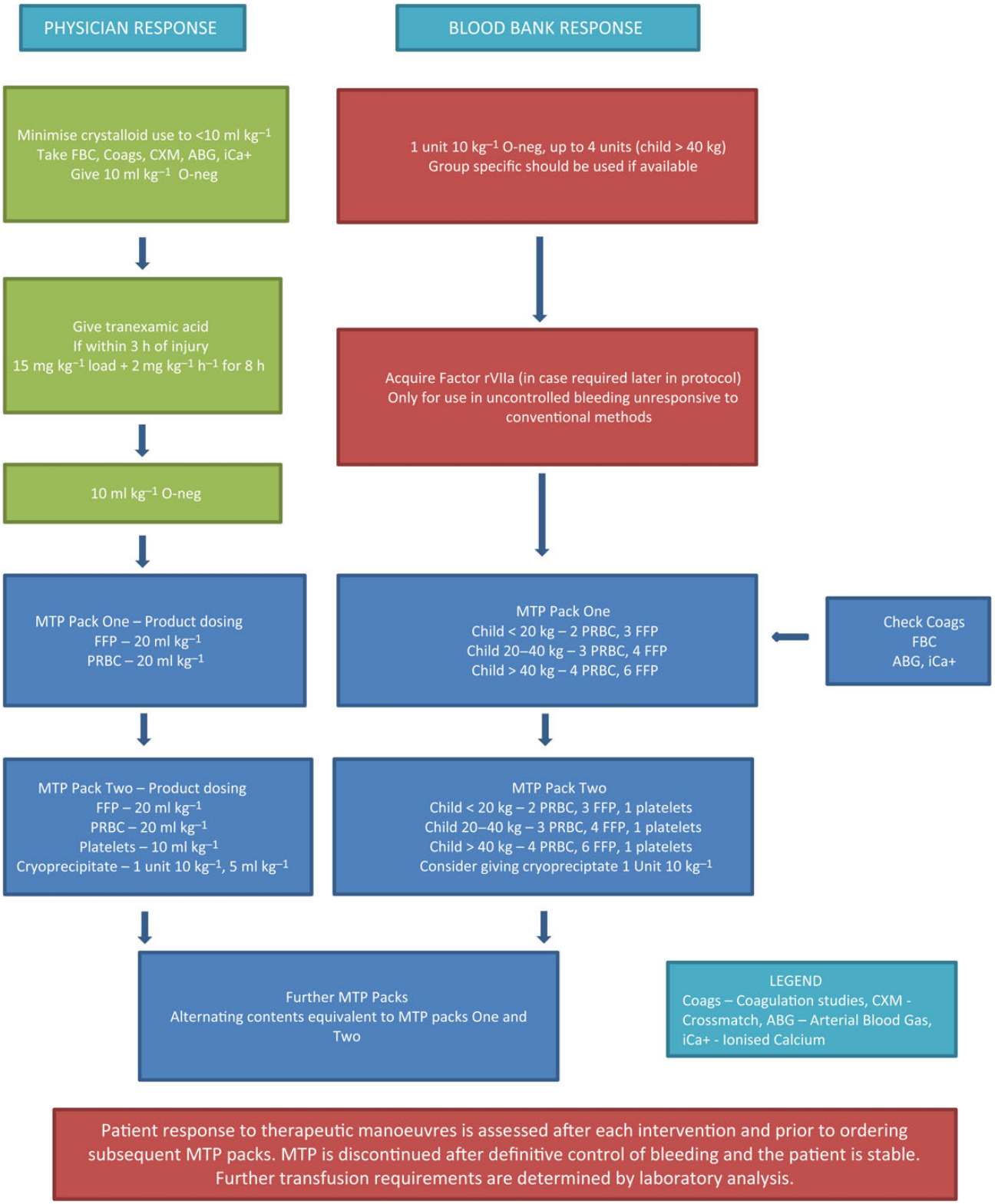

Fig 2 A sample paediatric MTP.[11]

Factor concentrates

The advent of individual factor concentrates and products containing specific factor combinations have raised the question of where they fit in the management of bleeding disorders, particularly during massive transfusion. The advantage of these preparations is that they exist in small volumes and may be useful for treatment of coagulopathy with avoidance of problems related to volume overload. This is likely to be of use in

correcting abnormalities in patients who are not actively bleeding and do not require concurrent volume resuscitation.

Fibrinogen is the precursor to fibrin and is cleaved by thrombin after the initiation, amplification, and propagation phases of the coagulation cascade. Fibrin is crucial in mediating Von Willebrand factor and platelet interactions, subsequently providing a catalytic surface for thrombin generation and clot formation after endothelial injury. If consumed or diluted as a result of trauma, during massive blood loss or transfusion, coagulation is impaired. It has been suggested that in the paediatric population, fibrinogen deficiency may develop more quickly than other factor deficiencies and that during massive blood loss and subsequent transfusion, it should be replaced early.[1] Obtaining laboratory fibrinogen levels is time-consuming and transfusion thresholds and dosing guidelines are not well established. During massive bleeding, a target level of >1.5–2 g litre^{-1} is suggested. One gram of fibrinogen administration increases plasma fibrinogen by ~0.25–0.28 g litre^{-1} in adult patients and each unit of FFP, cryoprecipitate, and fibrinogen concentrate contains 0.5, 0.3, and 0.9–1.3 g, respectively, of fibrinogen.[13] Studies have shown reduced transfusion requirements and mortality after its use in adult trauma patients. There may be benefit for its use in paediatric patients for the treatment of acquired hypofibrinogenaemia [loss or dilution coagulopathy, trauma, cardiac and thoracic surgery, liver failure, disseminated intravascular coagulation (DIC)]. The suggested fibrinogen concentrate dose is 70 mg kg^{-1}. Of note, the haemostatic efficiency of fibrinogen requires intact platelet activation, thrombin generation, and activated factor XIII-mediated polymerization. Consequently, the use of fibrinogen replacement during hyperfibrinolysis and DIC may be ineffective and require the use of anti-fibrinolytics such as TXA.[13]

The use of factor VIIa has been shown to improve the coagulopathy in adult patients with post-traumatic haemorrhage and decrease blood transfusion requirements. However, there is no evidence that it improves mortality and may increase the risk of thromboembolic complications.[1] Administration of factor VIIa is often included in massive transfusion protocols as a last resort to improve haemostasis. The recommended dose is 90 μg kg^{-1} for an adult patient, and varying studies looking at off-label dosing in paediatric patients after massive transfusion vary from 20 to 180 μg kg^{-1}.[1]

Prothrombin complex concentrate (PCC) is a preparation containing human plasma-derived vitamin K-dependent clotting factors II (prothrombin), VII, IX, and X. It has been used in the treatment of bleeding in congenital or acquired vitamin K-dependent coagulation deficiency and reversal of warfarin. There is little evidence in the literature on the use of PCC in the treatment of coagulopathy from uncontrolled bleeding in children, but it may offer an alternative to FFP if volume overload is of concern. If fibrinolysis or disseminated intravascular coagulation is present, the use of PCC is contraindicated. Owing to the prolonged half-lives of prothrombin and factor X (40–72 h), patients can become hypercoagulable and are at increased risk of thromboembolism.[13]

Tranexamic acid

TXA is a lysine analogue which inhibits fibrinolysis by binding to both plasminogen and plasmin, thereby reducing the breakdown of fibrin. The CRASH 2 trial in adult trauma patients demonstrated a reduction in mortality and bleeding, particularly if given early in the resuscitation process (<3 h from injury to treatment, preferably within 1 h from injury).[14] In paediatric patients, TXA is used to reduce the amount of bleeding in at-risk surgeries, including cardiac, craniofacial, and spinal. Dosing ranges vary, but it is suggested that timely administration of TXA within the first 3 h of trauma for children is beneficial. A loading dose of 15 mg kg^{-1} is given over 10 min and a maintenance infusion of 2 mg kg^{-1} h^{-1} for at least 8 h or until bleeding stops.[15] Similar dosing regimens have been used prophylactically for surgeries at high risk of bleeding.

Table 3 provides suggestions for dosing blood products, clotting factors, and TXA.

Table 3 Suggestions for dosing blood products, clotting factors, and TXA

Drug	Dosing
Cryoprecipitate	5–10 ml kg^{-1}
Fibrinogen concentrate	70 mg kg^{-1}
Prothrombin concentrate	25–50 IU kg^{-1}
Factor VII	90 μg kg^{-1}
Tranexamic acid	Loading dose 15 mg kg^{-1}, maintenance 2 mg kg^{-1} h^{-1} for 8 h (or bleeding cessation)

Conclusion

Massive haemorrhage in paediatric patients is a stressful and hazardous situation for all concerned. Management requires assessment of initial and ongoing blood loss with frequent evaluation of response to therapy. The aim is for resuscitation using adequate volume and composition of blood products to treat and prevent anticipated changes in coagulation. Massive transfusion protocols have been designed to ensure these requirements are met and have been shown to be feasible in paediatric practice. Point-of-care testing, using TEG and ROTEM, may provide a useful adjunct to laboratory testing to more quickly and accurately guide blood product use. TXA and single and multi-factor concentrates may be useful in the management of massive bleeding and therefore may warrant consideration in the development of future paediatric massive transfusion protocols.

Declaration of interest

None declared.

MCQs

The associated MCQs (to support CME/CPD activity) can be accessed at https://access.oxfordjournals.org by subscribers to *BJA Education*.

References

1. Diab Y, Wong E, Luban N. Massive transfusion in children and neonates. *Br J Haematol* 2013; **161**: 15–6
2. Lier H, Krep H, Schroeder S, Stuber F. Preconditions of hemostasis in trauma: a review. The influence of acidosis, hypocalcemia, anemia, and hypothermia on functional hemostasis in trauma. *J Trauma* 2008; **65**: 951–60
3. Paterson N. Validation of a theoretically derived model for the management of massive blood loss in pediatric patients—a case report. *Paediatr Anaesth* 2009; **19**: 535–40

4. Spinella PC, Holcomb JB. Resuscitation and transfusion principles for traumatic hemorrhagic shock. *Blood Rev* 2009; **23**: 231–40
5. Hendrickson JE, Shaz BH, Pereira G *et al*. Implementation of a pediatric trauma massive transfusion protocol: one institution's experience. *Transfusion* 2012; **52**: 1228–36
6. Reddick AD, Ronald J, Morrison WG. Intravenous fluid resuscitation: was Poiseuille right? *Emerg Med J* 2011; **28**: 201–2
7. Smith C, Wagner K. Principles of fluid and blood warming in trauma. *Int Trauma Care (ITACCS)* 2008; **19**: 71–9
8. Kuppurao L, Wee M. Perioperative cell salvage. *Contin Educ Anaesth Crit Care and Pain* 2010; **10**: 104–8
9. Livingston MH, Singh S, Merritt NH. Massive transfusion in paediatric and adolescent trauma patients: incidence, patient profile, and outcomes prior to a massive transfusion protocol. *Injury* 2014; **45**: 1301–6
10. PROMMTT Study Group. Defining when to initiate massive transfusion: a validation study of individual massive transfusion triggers in PROMMTT patient. *J Trauma Acute Care Surg* 2012; **74**: 59–68
11. Williams B. *Clinical Practice Guide—Blood and Blood Products* (Document ID 02901). Brisbane, Australia: Children's Health Queensland Hospital and Health Service, 2014
12. Afshari A, Wikkelso A, Brok J, Moller AM, Wettersley J. Thrombelastography (TEG) or thromboelastometry (ROTEM) to monitor haemotherapy versus usual care in patients with massive transfusion. *Cochrane Database Syst Rev* 2011; **16**: CD007871
13. Tanaka K, Esper S, Bollinger D. Perioperative factor concentrate therapy. *Br J Anaesth* 2013; **111**(Suppl. 1): i35–49
14. The CRASH-2 Collaborators. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. *Lancet* 2010; **376**: 23–32
15. Royal College of Paediatrics and Child Health. Evidence statement. Major trauma and the use of tranexamic acid in children. November 2012. Available from http://www.rcpch.ac.uk/system/files/protected/page/121112_TXA%20evidence%20statement_final%20v2.pdf