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Update on massive transfusion

H. P. Pham[1,2] and B. H. Shaz[1,3]*

[1] New York Blood Center, New York, NY, USA
[2] Department of Pathology and Cell Biology, Columbia University, New York, NY, USA
[3] Department of Pathology and Laboratory Medicine, Emory University, Atlanta, GA, USA

* Corresponding author. E-mail: bshaz@nybloodcenter.org

Editor's key points

- Optimal management of massive transfusion (MT) requires coordination between clinical, laboratory, and haematology teams.
- Early resuscitation using evidence-based MT protocols appears to improve outcome.
- Close monitoring of metabolic and coagulation function is essential to prevent the lethal triad of hypothermia, acidosis, and coagulopathy in massively bleeding patients.

Summary. Massive haemorrhage requires massive transfusion (MT) to maintain adequate circulation and haemostasis. For optimal management of massively bleeding patients, regardless of aetiology (trauma, obstetrical, surgical), effective preparation and communication between transfusion and other laboratory services and clinical teams are essential. A well-defined MT protocol is a valuable tool to delineate how blood products are ordered, prepared, and delivered; determine laboratory algorithms to use as transfusion guidelines; and outline duties and facilitate communication between involved personnel. In MT patients, it is crucial to practice damage control resuscitation and to administer blood products early in the resuscitation. Trauma patients are often admitted with early trauma-induced coagulopathy (ETIC), which is associated with mortality; the aetiology of ETIC is likely multifactorial. Current data support that trauma patients treated with higher ratios of plasma and platelet to red blood cell transfusions have improved outcomes, but further clinical investigation is needed. Additionally, tranexamic acid has been shown to decrease the mortality in trauma patients requiring MT. Greater use of cryoprecipitate or fibrinogen concentrate might be beneficial in MT patients from obstetrical causes. The risks and benefits for other therapies (prothrombin complex concentrate, recombinant activated factor VII, or whole blood) are not clearly defined in MT patients. Throughout the resuscitation, the patient should be closely monitored and both metabolic and coagulation abnormalities corrected. Further studies are needed to clarify the optimal ratios of blood products, treatment based on underlying clinical disorder, use of alternative therapies, and integration of laboratory testing results in the management of massively bleeding patients.

Keywords: massive transfusion; massive transfusion protocol; paediatric transfusion protocol; transfusion management

Management of patients requiring massive transfusion (MT) is challenging. Besides good clinical management and nursing care, it requires collaboration and effective communication between the clinical teams and the transfusion medicine service, which prepares and issues the blood products. Regardless of the aetiology of massive haemorrhage, the optimal strategy is to have a standardized management approach, such as an MT protocol (MTP), and to train the clinical and laboratory services potentially involved to be ready when a patient requires MT. MTPs should take into consideration not only transfusion of blood products, but use of laboratory tests, nursing care, and alternative therapies. This review focuses on the blood and blood-related transfusion management of patients requiring MTP. Most of the discussion below applies to trauma patients, as management of massive bleeding from other aetiologies follow the same general principles; potential differences are discussed where appropriate.

Definition of MT

MT refers to the transfusion of large volume of blood products over a short period of time to a patient who has severe or uncontrolled haemorrhage. MTPs describe an empirical treatment that optimizes management of resuscitation and correction of coagulopathy arising from severe haemorrhage. In adults, several definitions of MT exist based on the volume of the blood products transfused and also the time frames over which these transfusions occurred.[1–3] The three most common definitions of MT in adult patients are:[1 4 5]

(i) transfusion of $\geq$10 red blood cell (RBC) units, which approximates the total blood volume (TBV) (Table 1) of an average adult patient, within 24 h,
(ii) transfusion of $>$4 RBC units in 1 h with anticipation of continued need for blood product support, and
(iii) replacement of $>$50% of the TBV by blood products within 3 h.

Table 1 TBV estimation: TBV for adults based on Gilcher's rule of five for blood volume (in ml kg^{-1} body weight)

Patient	Fat	Thin	Normal	Muscular
Male	60	65	70	75
Female	55	60	65	70

Table 2 TBV estimation: TBV for paediatrics (in ml kg^{-1} body weight)

Patient	Estimation of TBV (ml kg^{-1} body weight)
Neonate (0–4 kg)	85
Infant (5–9 kg)	85
Young child (10–24 kg)	75
Older child (25–49 kg)	70
Young adult (≥50 kg)	Use Gilcher's rule in Table 1

The above definitions are only applicable for adult patients. Because of the age and weight variability in determining TBV in children (Table 2), paediatric patients require separate MT definitions. Recently, Diab and colleagues[4] suggested the following definition of MT in the paediatric population:

(i) transfusion of >100% TBV within 24 h,
(ii) transfusion support to replace ongoing haemorrhage of >10% TBV min^{-1}, and
(iii) replacement of >50% TBV by blood products within 3 h.

Epidemiology of MT

The need for MT occurs in a variety of clinical settings, such as trauma, obstetrics, and major surgery. Trauma-related mortality is the fourth leading cause of death in the USA, and according to the Centers for Disease Control and Prevention, unintentional injury accounted for more than 120 000 deaths in 2010.[6] About 40% of trauma-related mortality is due to uncontrolled bleeding. It has been estimated that among the injured patients admitted to trauma centres, up to 10% of military and up to 5% of civilian patients require MT.[7 8] In general, injury severity and transfusion requirement are associated with mortality. Most (99%) of the patients receiving <10 RBC units within the first 24 h survived, whereas only 60% of patients who received >10 RBC units within the first 24 h survived.[9] Obstetrical haemorrhage is another common cause of MT—massive haemorrhage is the most common cause of shock in obstetric patients and is the number one cause of maternal mortality worldwide.[10] Other causes of MT include gastrointestinal haemorrhage and major surgeries, such as cardiac, spinal, and liver surgery, and liver and multivisceral transplantation.

Pathophysiological changes as a result of massive haemorrhage and transfusion

The majority of the current understanding regarding the haemostasis and pathophysiological changes that occur during massive haemorrhage and the resultant MT are derived from animal and adult trauma patient studies.[4 11–13] The haemostatic defects in patients undergoing massive haemorrhage are dynamic and have multifactorial pathogenesis that relate to early trauma-induced coagulopathy (ETIC, also termed acute coagulopathy of trauma), transfusion of blood products, and infusion of crystalloids.[14] Historically, ETIC was attributed to crystalloid and RBC transfusion without administration of platelets, plasma, or both. However, subsequent studies in both adult and paediatric trauma patients demonstrated that ETIC was present in 24%, and up to 56% in severely injured patients, usually within 30 min of injury, even before receiving RBC and fluid resuscitation.[11 15–18] The presence of ETIC correlates with poor clinical outcomes independent of the severity of injury.[11 16–18] ETIC is associated with systemic anticoagulation and hyperfibrinolysis. In brief, tissue injury from trauma or surgery releases tissue factor, locally and subsequently systematically, which activates coagulation pathways. This initiation results in massive consumptive coagulopathy leading to a consumptive disseminated intravascular coagulation-like syndrome, which is most commonly seen in patients with severe head injury or extensive muscle damage.[19 20] Furthermore, hypoperfusion from massive haemorrhaging leads to thrombomodulin expression on endothelial cells.[11 21] Thrombin–thrombomodulin complex then activates protein C, which further limits coagulation by inhibiting activated factors V and VIII and enhancing fibrinolysis by depleting plasminogen activator inhibitor-1 (PAI-1) and accelerating plasmin formation. The diversion of thrombin from cleaving fibrinogen (for clot formation) to binding to thrombomodulin also reduces activation of thrombin-activatable fibrinolysis inhibitor (TAFI), which further leads to hyperfibrinolysis. The end result of these complex mechanisms is characterized by early coagulopathy due to systemic anticoagulation and hyperfibrinolysis.[22 23] In obstetric haemorrhage, hyperfibrinolysis is a prominent sign, both due to the above mechanism and to uterine atony, placental abruption, and accretism.[24]

In addition to ETIC and hyperfibrinolysis, further coagulopathy results from infusion of crystalloids, blood products, and severe anaemia. Massive haemorrhage leads to anaemia, which reduces primary haemostasis by impairing platelet adhesion and aggregation. The administration of RBC units without additional clotting factors or platelets during MT results in further impairment of haemostasis from both haemodilution (dilutional coagulopathy and thrombocytopenia) and metabolic derangement (acidosis and hypocalcaemia from citrate in storage solution, and hypothermia from refrigeration).[25–27] Acidosis and hypocalcaemia are detrimental to normal haemostasis.[27] Furthermore, hypothermia is associated with impairment of both platelet and coagulation factor activity.[4] All of these 'exogenous' factors contribute to the vicious cycle of progressive coagulopathy due to the 'lethal triad' of refractory coagulopathy, progressive hypothermia, and persistent metabolic acidosis (Fig. 1).[4]

Predicting MT

Early recognition and prompt treatment results in improved outcomes in massively bleeding patients. In many situations,

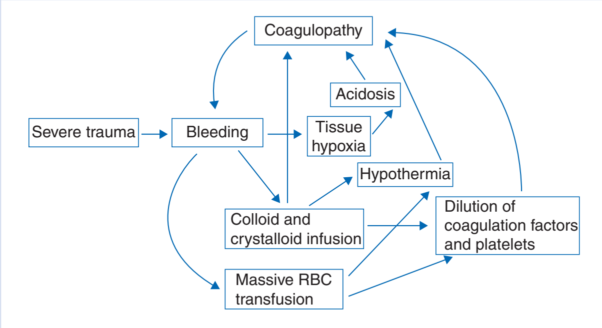

Fig 1 Pathogenesis of haemostasis abnormality in MT. Dilutional coagulopathy, activation of inflammatory mediators, hyperfibrinolysis, thrombocytopathy, and metabolic abnormalities (hypothermia, hypocalcaemia, and acidosis) all contribute to the pathogenesis of the haemostasis abnormality in massive haemorrhage.

it is unclear which bleeding patient will need MT. Models have been developed using both clinical and laboratory parameters to predict who would need MT in trauma patients;[28–35] however, none of them are a perfect tool.[36] For example, the Trauma Associated Severe Hemorrhage (TASH)-score incorporated seven clinical and laboratory variables (haemoglobin, base excess, systolic arterial pressure, heart rate, presence of free intra-abdominal fluid and/or complex fractures, and gender) into a composite score to predict the need for MT (defined in the study as administration of 10 or more RBC units within 24 h).[34] Nonetheless, Nunez and colleagues[35] demonstrated that simple and rapidly available parameters, such as the presence of penetrating trauma, systolic arterial pressure $<$90 mm Hg, heart rate $>$120 beats min^{-1}, and a positive focused abdominal sonography for trauma, appears to be as good as other more complex scoring systems to predict MT. If any two of the above four parameters are positive, the patient is likely going to require MT.

Clinical management in MT

In patients requiring MT, it is critical to maintain adequate blood flow and arterial pressure to maintain tissue oxygenation to vital organs. In the past, patients who are bleeding profusely, especially trauma patients, were initially given colloid or crystalloid fluid. Blood products were administered after 2 litre of fluid resuscitation, usually guided by laboratory results to keep haemoglobin $>$10 g dl^{-1}, platelet count $>$50 000 μl^{-1}, and INR $\leq$1.5. Using these guidelines, blood loss continued because of delay in laboratory turnaround time and dilutional coagulopathy. Mathematical consideration of resuscitation, studies highlighting increased morbidity and mortality with crystalloid use, recent military experiences, and better understanding the pathophysiology of ETIC has led to early use of RBCs, plasma, and platelets and reduced crystalloid use in resuscitation. Mathematical analysis of the available current component therapies in the USA suggested that when administering RBC, plasma, and platelets in a 1:1:1 ratio, this 645 ml product has a haematocrit of 29%, coagulation factor activity of 65%, and a platelet count of 90 000 μl^{-1}.[37] In addition, if storage defects are taken into account, then this mixed product would have a haematocrit of ∼26%, coagulation factor activity of 40–50%, and platelet count of 90 000 μl^{-1}.[37] Furthermore, any attempt to increase the concentration of one component would lead to dilution of the other two.

The administration of RBC:plasma:platelets at 1:1:1 ratio was first proposed by the US military and subsequently supported by military and then civilian studies. The rationale for the 1:1:1 ratio is that it more closely resembles whole blood, which would help to treat and prevent ETIC. A retrospective review of patients receiving MT at a US combat hospital demonstrated reduced mortality from 66% to 19% when the RBC:plasma ratio decreased from 8:1 to 2:1.[38] Then, Johansson and Stensballe[39] demonstrated that high plasma and platelet-to-RBC ratios improved survival in military traumatically injured patients with MT. However, these studies, and multiple others, are retrospective, and are therefore affected by survival bias. Survival bias is the bias resulting from the fact that surviving patients are more likely to receive more plasma and platelets in relation to RBCs compared with non-surviving patients because they lived long enough to receive those blood products. Thus, in June 2011, the Canadian National Advisory Committee on Blood and Blood Products determined that the retrospective evidence available at the time was insufficient to recommend a RBC:plasma:platelet transfusion ratio of 1:1:1 as the standard of care for MT in Canada. They also stated that subsequent retrospective studies would be unlikely to overcome survivorship bias and would not be able to make further contributions to the determination of the most effective ratio.[40] Recently, the Prospective Observational Multicenter Major Trauma Transfusion (PROMMTT) study examined the association between mortality rates in trauma patients and transfusion ratios; this cohort study demonstrated improved in-hospital mortality with RBC:plasma and RBC:platelet ratios $<$2:1 in the first 6 h.[41] The follow-up Pragmatic Randomized Optimal Platelet and Plasma Ratios (PROPPR) trial is a randomized trial to evaluate ratios, MT patients receive either a 1:1:1 (higher ratio) or a 2:1:1 (lower ratio) RBC:plasma:platelet with primary outcome of survival, and also complications and length of hospital stay. The results of this study should further elucidate the optimal ratios of blood product administration during MT.

Massive transfusion protocols

One way to coordinate the care for patients requiring MT is to develop an institutional MTP to facilitate communication between different services (trauma, nursing, transfusion medicine, and other laboratories), avoid delay in clinical care, laboratory testing and blood product transfusion, and nursing care. MTP is a way to assure good patient care by having a standard protocol on specific actions to take for each service involved. MTPs have demonstrated improved patients survival and reduced rates of organ failure and post-trauma complications.[29] The development, implementation, and continuous improvement of an MTP require ongoing collaboration

Table 3 Sample adult MTP. Modified from Table 2 in Cushing and Shaz,[44] with permission from Minerva Anestesiologica, Edizioni Minerva Medica S.p.A. RBC, red blood cell; SDP, single-donor platelets; Cryo, cryoprecipitate; rFVIIa, recombinant activated factor VII; AB, blood type AB

Study	Package 1	Package 2	Package 3	Comments
Cotton and colleagues[43]	10 RBC units 4 AB plasma units 2 SDP units	6 RBC units 4 plasma units 2 SDP units	Repeat package 2	Cryo will be given upon physician's request
Dente and colleagues[45]	6 RBC units 6 AB plasma units	6 RBC units 6 plasma units 1 SDP unit	6 RBC units 6 plasma units 10 cryo units	rFVIIa will be considered upon physician's request
O'Keeffe and colleagues[47]	5 RBC units 2 AB plasma units	5 RBC units 2 plasma units 1 SDP unit	5 RBC units 2 plasma units 10 cryo units rFVIIa	
Nunez and colleagues[46]	10 RBC units 6 AB plasma units 2 SDP units	Repeat package 1	Repeat package 1	
Riskin and colleagues[48]	6 RBC units 4 plasma units 1 SDP unit	Repeat package 1	Repeat package 1	rFVIIa will be considered after 2 rounds of blood products given

between different clinical services. When developing an MTP, determining quality indicators will enable clear parameters to track and trend, such as the time for products preparation and issue, product wastage, laboratory turnaround time, laboratory values, and indications for MTP in order to continuously improve the MTP. An MTP should have the following components:

(i) When and who should initiate MTP.
(ii) Notification of the transfusion service and laboratory regarding start and stop of MTP.
(iii) Laboratory testing algorithm [prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen level, blood gas, and complete blood count], and thromboelastography if available.
(iv) Blood product preparation and delivery (i.e. predetermined transfusion packages).
(v) Other patient care needs (such as blood warmers, nursing care).

MTPs can include preparation and administration of blood products based on laboratory test results, predetermined transfusion packages [see Table 3 (adult MTPs) and Table 4 (paediatric MTPs), for examples), or integration of both.[42] Although the number and timing of blood component delivery, laboratory testing algorithms, and other aspects of the MTPs varies between institutions, most current MTPs use predetermined transfusion packages.[42] MTPs vary in their predetermined transfusion packages, but all include platelet and plasma units with RBC units (Table 3).[43–48] Furthermore, patients with obstetrical haemorrhage should also be monitored closely for fibrinogen level, because it has been shown that women with fibrinogen level >400 mg dl^{-1} did not develop post-partum haemorrhage. Similarly, data from neurology and cardiac surgery showed that there is increased bleeding tendency if the fibrinogen level is <150–200 mg dl^{-1}.[49 50] Moreover, a retrospective review from a US Army hospital demonstrated that increasing the ratio of fibrinogen:RBC is associated with improved survival to hospital discharge by decreasing death from bleeding.[51] Thus, monitoring fibrinogen level and/or early transfusion of fibrinogen concentrate or cryoprecipitate could be potentially beneficial.

The military uses fresh whole blood when apheresis platelet products are not available. In the recent military experiences in Iraq and Afghanistan, whole blood transfusion compared with RBC, plasma, and apheresis platelet use reduced pulmonary and tissue oedema, which decreased the ventilation time and also allowed closure of the abdomen with minimal delay.[52] Furthermore, retrospective analysis suggested that patients who received both fresh whole blood and component therapy had better clinical outcomes compared with those who received only component therapy.[53] However, concern for transfusion-transmitted infections and transfusion-associated graft *vs* host disease remains.[54 55]

Paediatric MTPs

The data on paediatric MTPs are limited, and thus practices vary significantly among institutions.[56 57] Owing to logistics, it is a challenge for hospitals that are not free-standing children's hospitals to have both adult and paediatric MTPs. In the majority of institutions, a single MTP is used for both adult and paediatric patients.[4] Two published studies on paediatric MTPs did not show improvement in mortality in the group receiving blood products according to the institutional MTP compared with the historical control[58] or the group receiving blood products at physician discretion (Table 4).[59] Despite obtaining null results in both studies, probably due to small sample sizes,[58 59] it was suggested that implementation of MTP to increase the plasma:RBC ratio is feasible in paediatric patients.[58]

Considerations for MTP development

When developing an MTP, it is important that an institution establishes policies for emergency release and delivery of blood products. There should also be protocols for administration

Table 4 Sample paediatric MTPs.[4] Modified from Table 2 in Diab *et al*,[4] with permission from *British Journal of Haematology*, John Wiley and Sons. *Difference from protocol in Diab and colleagues[4] comparing with protocol from Hendrickson and colleagues.[58] Hendrickson and colleagues'[58] protocol does not contain emergency release package. RBC, red blood cell; Cryo, cryoprecipitate

Package	RBC	Plasma	Platelets	Cryo
Neonate (0–4 kg)				
Emergency release	½ unit			
2	½ unit	½ unit	2 units (3 units*)	
3	½ unit	½ unit		2 units (1 unit*)
4	½ unit	½ unit	2 units (3 units*)	
5	½ unit	½ unit		2 units (1 unit*)
Infant (5–9 kg)				
Emergency release	1 unit			
2	1 unit	1 unit	3 units	
3	1 unit	1 unit		3 units (2 units*)
4	1 unit	1 unit	3 units	
5	1 unit	1 unit		3 units (2 units*)
Young child (10–24 kg)				
Emergency release	2 units			
2	2 units	2 units	4 units (6 units)	
3	2 units	2 units		4 units
4	2 units	2 units	4 units (6 units)	
5	2 units	2 units		4 units
Older child (25–49 kg)				
Emergency release	3 units			
2	3 units	3 units	6 units	
3	3 units	3 units		6 units
4	3 units	3 units	6 units	
5	3 units	3 units		6 units
Adolescent (≥ 50 kg)				
Emergency release	5 units			
2	5 units	5 units	6 units	
3	5 units	5 units		8 units
4	5 units	5 units	6 units	
5	5 units	5 units		8 units

of D-positive RBCs to a D-negative or unknown patient, issuing ABO-incompatible plasma, and administration of antigen-positive or untested RBCs to a patient with the corresponding red cell alloantibody. It is also important to follow patient identification protocols in order to avoid ABO incompatible transfusion errors. In many trauma situations, there is excessive blood loss, and transfusion is needed before the ability to perform pre-transfusion testing. In these cases, group O RBCs and AB plasma products should be given until the patient's blood type can be determined. Alternatively, it has been demonstrated that using group A plasma products in trauma patients needing emergency plasma transfusion due to limited supply of group AB plasma did not result in an increase in mortality or incidence of complications, such as haemolytic reaction.[60] It is important to obtain and test a patient sample as soon as possible after admission so that type-specific products can be administered when available. This helps to preserve the inventory of group O RBCs and AB plasma, and minimizing potential for ABO typing discrepancies when a patient has received multiple units of group O RBCs and AB plasma. However, if type-specific products are administered, adequate patient identification steps should be in place to ensure ABO mistransfusion does not occur.

The frequency of anti-D formation after transfusion of D-positive blood products to a D-negative patient is about 20% for RBCs and <4% for platelets (likely lower for apheresis platelets).[61–63] It is especially important to prevent anti-D formation in females of childbearing potential because anti-D can cause haemolytic disease of the fetus and newborn in future pregnancies. Therefore, females of childbearing potential should receive D-negative RBCs. However, institutions may transfuse D-positive RBCs to a D-negative/D-unknown female of childbearing potential after a certain number (such as 8 units) of D-negative RBCs have already been transfused given the balance of available inventory and the likelihood of survival. Each institution should have a policy determining the use of D-positive products in D-negative or D-unknown patients, including the use of D-positive products for men and women past childbearing age (usually >50 yr old), and after a set number of D-negative RBC units. In addition, Rh immune globulin (RhIG) might be considered to prevent anti-D alloimmunization in D-negative patients receiving D-positive blood products. The practice of giving RhIG is more common when D-positive platelets are given to D-negative patients. The risk of haemolysis needs to be weighed against the benefit of prevent alloimmunization, especially when RhIG is given to a patient receiving more than 1 or 2 D-positive RBC units.

Another important consideration is availability of thawed plasma units for patients requiring MT. It takes about 20 min to thaw frozen plasma. Expedited plasma transfusion in patients requiring MT can result in reduced overall transfusion requirement and mortality.[64] Hence, in order to facilitate early transfusion of plasma in the resuscitation process, many institutions keep some units of thawed plasma available for immediate issue. Many trauma patients arrive in the trauma bay with unknown blood type; thus, AB plasma is prepared since it is the universal donor type. However, AB plasma is rare since only 4% of the population is group AB. Once plasma is thawed, it can only be kept for 5 days. Therefore, it might be a challenge for some institutions to maintain an inventory of thawed AB plasma at all times. Thus, some institutions use group A plasma (some with anti-B titre <100) during the initial plasma transfusion while waiting for the patient's ABO type and having group B and O plasma thawed for subsequent plasma orders.[65] Another option would be maintaining an inventory of liquid AB plasma. Liquid AB plasma is preserved in citrate–phosphate–dextrose and has a 26 day expiry date. Potential drawbacks for using liquid plasma are the presence of lymphocytes and RBC in those units and lower factor levels in the product, leading to the risk of transfusion-associated graft *vs* host disease and possible D sensitization if D incompatible transfusions are given. Goodnough and colleagues[66] suggested using irradiated liquid plasma as part of the MTP in order to allow availability of plasma for immediate use in patients requiring MT. The choice of how much plasma, the blood type mix, and which type of plasma depends on the institution's volume and transfusion needs.

Alternative medications included in MTP

Recombinant activated factor VII (rFVIIa) is approved by the US Food and Drug Administration to treat bleeding in patients with congenital factor VII deficiency and patients with haemophilia A or B who have inhibitors against factor VIII or IX, respectively. However, it has been used off-labelled in many settings involving MT. In several clinical trials in patients with trauma or undergoing surgery, rFVIIa has not been shown to improve clinical outcomes.[67–69] Furthermore, rFVIIa has been associated with thrombotic risk.[70 71] Therefore, the risk and benefit of using rFVIIa in patients with MT are unclear currently. A few experts suggest that rFVIIa should be removed as an adjunctive therapy from an institutional MTP.[72] If a physician would like to use rFVIIa as an adjunctive therapy, it should be given as early as possible at a time when haemostasis has not been severely compromised.[73]

Prothrombin complex concentrate (PCC) has been used to treat congenital coagulation disorders and for warfarin reversal in patients with active bleeding or undergoing urgent procedures. PCC contains factors II, VII, IX, and X, and proteins C and S, with variations in the amount of factors between different products; thus, it is important to know which PCC product is available at the institution. PCC can be three-factor, such as Profilnine SD (Grifols Biologicals, Los Angeles, CA, USA) (lacking factor VII), or four-factor, such as Kcentra (CSL Behring, King of Prussia, PA, USA). To date, there has not been any prospective randomized controlled trial to evaluate the efficacy and safety of PCC in massively bleeding patients. In addition, PCC might be associated with thromboembolic risk as shown in animal studies.[74 75] Hence, it is advisable to discuss the risks and benefits of using PCC as an adjunctive therapy in any institutionally MTP and it is recommended that PCC usage should be continually evaluated.

In several small prospective studies, fibrinogen concentrate has been shown to reduce peri-operative bleeding and transfusion requirement.[76–79] Fibrinogen concentrates, in conjunction with PCC, also have been shown in a few prospective studies to decrease the transfusion requirements and mortality in trauma patients.[80 81] In the USA, fibrinogen concentrate (RiaSTAP, CSL Behring) is approved for the treatment of patients with congenital fibrinogen deficiency. It has not been approved to be used as an adjunctive therapy in patients requiring MT. Therefore, it is recommended to discuss the risk and benefit of using fibrinogen concentrate as part of the MTP in any institution (see Tanaka and colleagues,[82] this issue, for further discussion).

Antifibrinolytic agents, such as tranexamic acid (TXA), were demonstrated to reduce mortality in trauma patients in both civilian[83] and military settings,[84] especially if given early in the resuscitation process (<3 h from injury to treatment, preferably within 1 h from injury).[85] In the military setting, the MATTERs study demonstrated that although patients receiving TXA were more severely injured, mortality in the TXA group was lower than in the group not receiving TXA.[84] Moreover, TXA was shown to be a cost-effective therapy in all low-, middle-, and high-income countries using data from the randomized controlled CRASH-2 trial done in a civilian population.[86] It has also been suggested that TXA reduces blood loss at the time of Caesarean section and the risk of progression to severe postpartum haemorrhage.[87 88] A randomized controlled trial is currently ongoing to access the effect of TXA in treating postpartum haemorrhage. Smaller studies also showed that TXA reduced blood loss in paediatric patients undergoing cardiac[89] or scoliosis surgery.[90] Therefore, it is recommended that TXA should be part of the early resuscitation process.

Laboratory monitoring during MTP

MTP requires adequate laboratory support to oxygen-carrying capacity, haemostasis, and metabolic status in order to address and correct abnormalities. In addition, laboratory results can be used retrospectively to assess the need for MTP adjustment. For example, if all patients have low fibrinogen values upon intensive care unit admission, increased cryoprecipitate or fibrinogen concentrate use is indicated during MTP. A metabolic panel should be used to monitor metabolic abnormalities during MT, such as hyperkalaemia and hypocalcaemia. Point-of-care arterial blood gases measurement is helpful in monitoring oxygenation.

Monitoring haemostasis in patients with MT is challenging because there is no validated coagulation assay that can detect accurately the coagulopathies in massively bleeding patients in a timely manner. Conventional coagulation assays, such as PT, aPTT, and fibrinogen levels, are likely not available in real-time fashion. In addition, these tests do not detect some haemostatic abnormalities, such as platelet dysfunction, hyperfibrinolysis, and factor XIII deficiency. They also do not quantify the relative contribution of pro-coagulant and anti-coagulant factors.[91 92] Although these conventional coagulation assays do not predict the future need for MTP and have limited utility to direct ongoing blood component therapy in real time because of slow turnaround times,[93] they should be ordered and retrospectively reviewed to help in correcting any abnormalities occurring during the resuscitation and to continuously improve the institutional MTP.

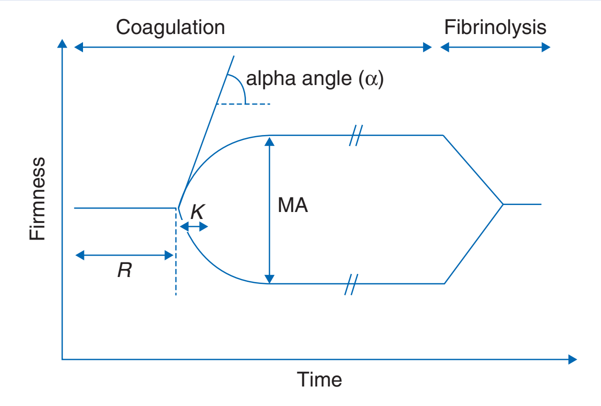

Fig 2 TEG tracing. Modified from Figure 1 in Cushing and Shaz,[44] with permission. *R*, reaction time; *K*, kinetics time; MA, maximum amplitude.

Recently, it has been suggested that point-of-care haemostasis assays, such as thromboelastography (TEG) and rotational thromboelastometry (ROTEM), might be better at assessing coagulopathy in patients requiring MT.[94] These assays offer clinicians a graphic representation of the coagulation process (Fig. 2). In addition, the parameters obtained from TEG/ROTEM could provide a quantitative measure of individual components of the haemostatic process in adult patients (Table 5). Hence, the use of TEG/ROTEM can provide information to guide blood component therapies in a more timely manner.[94] There are several advantages of using TEG/ROTEM.[4] First, the turnaround time for these assays is shorter compared with conventional assays (15–30 min); thus, they can be used in

Table 5 TEG/ROTEM parameters, interpretations, and management of haemostatic abnormalities.[4] Modified from Table 3 in Diab and colleagues,[4] with permission from *British Journal of Haemotology*, John Wiley and Sons. *R*, reaction time; CT, clotting time; *K*, kinetics time; CFT, clot formation time; α, alpha angle; MA, maximum amplitude; MCF, maximum clot firmness; LY, lysis; ML, maximum lysis

TEG parameter	ROTEM parameter	Definition	Haemostatic phase	Aetiologies for abnormalities	Potential management
R	CT	Time from the start of the test till the first sign of clot formation	Initiation of coagulation	Prolonged *R*/CT: factor deficiencies or anticoagulants. Shortened *R*/CT: plasma hypercoagulability	Plasma for prolong *R*/CT
K	CFT	Time from the start of clot formation to the time when the curve reaches amplitude of 20 mm	Amplification of coagulation	Prolonged *K*/CFT: factor deficiencies, hypofibrinogenaemia, dysfibrinogenaemia, thrombocytopenia, or platelet dysfunction	Cryoprecipitate
α	α	Angle between the baseline and the tangent to the curve through the starting point of coagulation	Propagation of coagulation (i.e. 'thrombin burst')	Low α: factor deficiencies, hypofibrinogenaemia, dysfibrinogenaemia, thrombocytopenia, or platelet dysfunction	Cryoprecipitate
MA	MCF	Amplitude measured at the maximum curve width	Propagation of coagulation (i.e. 'platelet=fibrin interaction')	Low MA/MCF: factor XIII deficiency, hypofibrinogenaemia, dysfibrinogenaemia, thrombocytopenia, or platelet dysfunction	Platelets might consider plasma or cryoprecipitate for factor XIII deficiency if ongoing bleeding and persistently low MA/MCF
LY	ML	Reduction in area under the curve (LY) or in amplitude (ML) from time MA/MCF is achieved until 30 or 60 min after MA/MCF	Fibrinolysis	Increased LY/ML: hyperfibrinolysis	Anti-fibrinolytic medication

combination with clinical assessment for the decision-making process.[95] Secondly, these assays can detect hyperfibrinolysis, an important component of haemostatic abnormalities in patients with MT that cannot be detected by PT and aPTT assays.[94] Thirdly, unlike the PT and aPTT that can only test secondary haemostasis, whole blood assays assess all phases of coagulation, such as the contribution of platelets to primary haemostasis and factor XIII to cross-linking the fibrin clot. Fourthly, TEG/ROTEM can be performed at the patient's true temperature, which makes it more sensitive for detection of coagulopathy due to hypothermia.[96] TEG/ROTEM has been shown to reduce the transfusion requirement and need of MT in patients undergoing cardiovascular and liver transplantation surgery.[97–100] Nonetheless, a Cochrane review suggested that there is no evidence that TEG/ROTEM reduced the morbidity and mortality in MT patients.[101] There is no universal agreement on the use of TEG/ROTEM to monitor and direct component therapy in patients with MT.

Complications from MT

Besides the risk of transfusion reactions that occur with single unit transfusions, patients with MT are at risk of other adverse events due to large transfusion volumes, such as hypocalcaemia and acidosis due to citrate and hypothermia due to cold storage (Table 6).[4] The patient should be monitored closely for these complications because they might contribute further to coagulopathy. Paediatric patients, patients with pre-existing cardiac, hepatic, and renal disease, or older patients are more at risk for having these complications.

Another potential risk is the use of stored RBCs, although no randomized controlled trial has demonstrated an association

Table 6 Complications from MT.[4] Modified from Table 1 in Diab and colleagues,[4] with permission from *British Journal of Haemotology*, John Wiley and Sons. *Adverse events more likely, due to rapid infusion of a large amount of blood products in a short period of time

Adverse events	Comments and potential treatments
Transfusion reactions	
Allergic	Range from simple urticarial to anaphylaxis. Steroid and diphenhydramine might be given to patients with allergic transfusion
Haemolytic transfusion reaction (acute and delayed)	Might be reduced by giving group O RBCs and AB plasma for emergency release of blood products
Febrile non-haemolytic transfusion reaction	Diagnosis of exclusion
Immunological reactions	
Transfusion-related acute lung injury (TRALI)	Incidence can be reduced by transfusing male-only plasma
Transfusion-related immunomodulation (TRIM)	Might be responsible for increased risk of bacterial infection
Transfusion-associated graft *vs* host disease (Ta-GVHD)	Irradiation of cellular blood products in patients at risk (such as neonates and immunosuppressed patients) to prevent Ta-GVHD
Post-transfusion purpura (PTP)	Can be treated with IVIg infusion, steroid, or plasma exchange
Metabolic complications	
Hypocalcaemia*	Because of citrate overload from rapid transfusion of blood products. Neonates and patients with pre-existing liver disease are at risk for hypocalcemia. Monitor ionized calcium level and correct if necessary
Hypomagnesaemia*	Because of large volume of magnesium-poor fluid and citrate overload. Monitor ionized magnesium level and correct if necessary
Hyperkalaemia*	Because of haemolysis of RBC from storage, irradiation, or both. Neonates and patients with pre-exisiting cardiac and renal diseases are at risk for hyperkalaemia. Monitor potassium level and correct if necessary. Fresh RBCs (<5–10 days old), irradiated <24 h before transfusion or washing may decrease risk
Hypokalaemia*	Because of re-entry into transfused RBCs, release of stress hormones, or metabolic alkalosis. Monitor potassium level and correct if necessary
Metabolic alkalosis*	Because of citrate overload. Monitor acid–base status
Acidosis*	Because of hypoperfusion, liver dysfunction, and citrate overload. Monitor acid–base status
Hypothermia*	Because of infusion of cold fluid and blood products, opening of body cavities, decrease heat production, and impaired thermal control. Neonates and infants are at increased risk. Blood warmer should be used
Other adverse events	
Haemostatic defects*	Result from complex mechanism (discuss in the pathophysiology section)
Infection	Can result from blood products or other resuscitated procedures, such as surgeries
Transfusion-associated circulatory overload (TACO)*	Should be differentiated from TRALI. Infants and patients with pre-existing cardiac disease are at increased risk. Oxygen and diuresis can be used
Air embolism	A rare fatal complication. Instructions and/or protocols on how to use rapid infuser must be followed

of red cell storage age and patient outcome. A recent meta-analysis investigating the effect of storage lesions of RBCs suggested that using older stored RBC units was associated with increased mortality.[102] However, the majority of data in this meta-analysis was from retrospective observational studies. A recent large randomized controlled trial done in premature, very low-birth-weight infants (the ARIPI trial) did not find an association between using fresh RBCs and improved mortality.[103] Several other trials (such as the RECESS trial) are ongoing at the time of writing to investigate the storage effect of RBCs, on clinical outcome of transfusion (see Cohen and Matot,[104] this issue, for further discussion).

Conclusions

For optimal management of massively bleeding patients, effective communication between the transfusion and other laboratory medicine services and clinical teams is essential. It is important for the transfusion medicine service to prepare necessary blood products while managing the blood inventory. A well-defined MTP is a valuable tool for institutions, especially for institutions that have an active trauma, high-risk pregnancy, cardiac surgery, and/or transplantation service, as it can delineate how blood products are ordered, prepared, and delivered, determine laboratory algorithms to use as transfusion guidelines, and facilitate communication between the transfusion service and clinical team. Instructions regarding nursing care and specific duties for other allied health personnel should be in the protocol. Early transfusion of platelets, plasma, and RBCs to trauma patients in a ratio approaching 1:1:1 might be beneficial in reducing mortality and improving patient outcome; however, further prospective randomized clinical trials will be useful in determining the optimal ratio. TXA improved survival in several randomized controlled trials in patients with MT, and thus, should be used during the resuscitation process. There is also evidence that other medical interventions or products, such as TEG/ROTEM and PCC, might improve patient outcome when used in combination with an MTP. The guidelines for MTP have been changing in recent years with the completion of several studies, and likely will continue to evolve as future studies are completed. These will further clarify the ideal ratios of blood products, patient-specific modifications, and other measures that should be taken in the management of massively bleeding patients.

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