British Journal of Anaesthesia **111** (S1): i71–i82 (2013)
doi:10.1093/bja/aet376

BJA

Update on massive transfusion

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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,