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REVIEW

Massive transfusion protocols: current best practice

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Abstract: Massive transfusion protocols (MTPs) are established to provide rapid blood replacement in a setting of severe hemorrhage. Early optimal blood transfusion is essential to sustain organ perfusion and oxygenation. There are many variables to consider when establishing an MTP, and studies have prospectively evaluated different scenarios and patient populations to establish the best practices to attain improved patient outcomes. The establishment and utilization of an optimal MTP is challenging given the ever-changing patient status during resuscitation efforts. Much of the MTP literature comes from the trauma population, due to the fact that massive hemorrhage is the leading cause of preventable trauma-related death. As we come to further understand the positive and negative clinical impacts of transfusion-related factors, massive transfusion practice can be further refined. This article will first discuss specific MTPs targeting different patient populations and current relevant international guidelines. Then, we will examine a wide selection of therapeutic products to support MTPs, including newly available products and the most suitable of the traditional products. Lastly, we will discuss the best design for an MTP, including ratio-based MTPs and MTPs based on the use of point-of-care coagulation diagnostic tools.

Keywords: hemorrhage, MTP, antifibrinolytics, coagulopathy, trauma, ratio, logistics, guidelines, hemostatic

Introduction and definition of massive transfusion

The importance of prompt blood replacement in the setting of uncontrolled hemorrhage is well established and intuitively practiced to resuscitate exsanguinating patients. During combat, trauma-associated hemorrhage due to penetrating or blunt injury is often supported by transfusion of whole blood (WB) collected directly from other soldiers. This historical military practice has evolved into a bleeding management strategy for hemorrhagic shock known as damage control resuscitation in the civilian setting. While the military massive transfusion (MT) practices have been refined to improve outcomes over time, the difference in the types of traumatic or non-traumatic injuries, patient health conditions, availability of blood products, and provider-related factors must be considered before applying the same MT practices to a civilian setting.[1,2] The objective of this article is to provide guidance on how to optimize massive transfusion protocols (MTPs) in the trauma and non-trauma settings. We will define MT and discuss different types of MTPs, review expert guidelines available for MTPs, provide guidance for the use of therapeutic hemostatic products, discuss the relevance of point-of-care (POC) coagulation testing and blood product ratios during an MTP, and finally conclude with practical logistical and safety considerations maximize an MTP.

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Definition of MT

MT is defined when either 1) total blood volume is replaced within 24 hours, 2) 50% of total blood volume is replaced within 3 hours, or 3) rapid bleeding rate is documented or observed. Rapid bleeding rate in adults can be defined as more than 4 units of red blood cells (RBCs) transfused within 4 hours with active major bleeding or more than 150 mL/minute of blood loss. The definition of MT in children is slightly different from the definition in adults but is beyond the scope of this review.[3,4]

Types of MTPs

Trauma MTPs

At the onset of severe traumatic bleeding, aggressive fluid replacement and rapid mechanical/surgical bleeding control can often mitigate the extent of tissue injury, inflammation, and hypoperfusion. However, untimely or incomplete control of massive bleeding can lead to systemic consumptive coagulopathy with hemodilution and endothelial damage.[5,6] If the systemic damage remains uncorrected, concurrent trauma-associated hypothermia and acidosis can further exacerbate coagulopathy and lead to irreversible multiorgan failure (MOF). In addition, older age (>55 years old), high injury severity score (ISS>15), high base deficit (>8 mEq/L), high lactate (>2.5 mmol/L), and blood transfusion have been observed as independent risk factors for MOF in both retrospective and prospective studies.[7,8] Catastrophic exsanguination is the second leading cause of death during traumatic injury; thus, the resuscitative goal of MT includes rapid hemostasis and maintenance of adequate tissue oxygenation to prevent end organ damage. Various MT algorithms have been published and depend on a hospital's capabilities and preferences (Table 1).

Non-trauma MTPs

Refractory bleeding due to medical illness or surgical procedures often requires significant fluid replacement, including blood product transfusion, to resuscitate patients. Various clinical settings, such as gastrointestinal bleeding, intracranial bleeding, vascular surgical bleeding, and general surgical bleeding, are common indications for non-trauma MTPs when massive hemorrhage definitions are met. Many times trauma MTP algorithms are usually adopted fully or with minimal modifications in the non-trauma setting given the ease of transferring this practice. However, the optimal algorithm has not been impartially established or prospectively validated. A retrospective study showed that the use of an MTP in a non-trauma setting was associated with poor clinical outcomes, most probably related to underlying disease, not the MTP itself.[9,10] However, this study and a similar retrospective study[10] both observed that non-trauma MTPs were over-activated more than 50% of the time without subsequent MT. In one of the studies examining blood product wastage, platelet wastage was significantly higher in non-trauma MTPs versus trauma MTPs (12.8% versus 8.1%).[10] Prospective studies are clearly needed to optimize non-trauma MTPs, including validation of different ratios and development of screening/prediction tools to determine which patients would most benefit from an MTP.

Current MT guidelines

Guidelines are designed to provide evidence-based, well-balanced information regarding the benefits and limitations of therapeutic interventions. Two major guidelines are available for MT: the European guidelines by the Task Force for Advanced Bleeding Care in Trauma (updated in 2013) and the Trauma Quality Improvement Program (TQIP) recommendations from the American College of Surgeons.[11] The Task Force has included a new dedicated section discussing the implementation and adherence to evidence-based, protocolized clinical practices relating to blood transfusion in bleeding trauma patients. Notably, a significant portion of these guidelines is dedicated to a discussion of the utility of rapid and pertinent laboratory tests, evaluation of clinically significant hemorrhage, and administration of appropriate blood products for resuscitation in a timely manner. Similarly, the 2011 update on the clinical practice guidelines for blood conservation from the Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists also advocates the judicious use of blood products, factor concentrates, hemostatic agents, and blood salvage to minimize blood loss.[12] In addition, the American College of Surgeons has established the TQIP to provide recommendations for the care provided to trauma patients. It also provides guidelines for MTPs, which emphasize tight collaboration among blood banks, emergency departments, anesthesiologists, and trauma services. TQIP recommends that an MTP needs to define protocol triggers for activation/deactivation, an algorithm for preparation and delivery of blood products, including continued support in the non-emergency department (ED) setting. The guidelines advocate the establishment of transfusion targets, recommend the use of pharmacologic hemostatic agents, and suggest ongoing evaluation of cumulative MTP performance. A recent survey by TQIP evaluated over 180 registered trauma centers on their current MTP practices (Table 2).[13]

Table 1 Published patient-cohort specific massive transfusion protocols

Source (year)	Package 1	Package 2	Package 3	Note
Adult MTP				
O'Keeffe et al[85] (2008)	5 RBCs, 2 AB TP	5 RBCs, 2 TP, 1 SDP	5 RBCs, 2 TP, 10U cryo, FVIIa	
Cotton et al[86] (2009)	10 RBCs, 4 AB TP, 2 SDP	6 RBCs, 4 AB TP, 2 SDP	Repeat package 2	Cryo with physician request
Dente et al[87] (2009)	6 RBCs, 4 AB TP	6 RBCs, 6 TP, 1 SDP	6 RBCs, 6 TP, 10U cryo	rFVIIa at clinician discretion
Riskin et al[88] (2009)	6 RBCs, 4 FFP, 1 SDP	Repeat package 1	Repeat package 1	Consider rFVIIa after 2 rounds
Nunez et al[89] (2010)	10 RBCs, 6 AB TP, 2 SDP	Repeat package 1	Repeat package 1	
Tan et al[90] (2012)	4 RBC, 4 AB FFP	4 RBC, 4 AB FFP	4 RBC, 4 AB FFP, 2 SDP	rFVIIa is considered for refractory bleeding and is at trauma team's discretion
Ball et al[91] (2013)	6 RBCs, 6 plasma	6 RBCs, 6 plasma, 1 SDP	6 RBCs, 6 plasma, 20U cryo	Consider rFVIIa after 2 rounds (abdominal surgery)
Bawazeer et al[92] (2015)	6 RBCs, 4 AB FFP, 1 SDP	4 RBCs, 4 FFP	Repeat package 2	10U cryo when fibrinogen <1.5 g/L, and rFVIIa is at physician's discretion
Maciel et al[93] (2015)	6 RBCs, 4 FFP, 1 SDP	RBC:FFP (1:1) plus cryo and SDP	Repeat package 2	rVIIa and TXA are at physician's discretion (abdominal aoritic injury)
Pediatric/adolescent MTP				
Riskin et al[88] (2009)	4 RBCs, 2 FFP, 1 SDP	Repeat package 1	Repeat package 1	Consider rFVIIa after 2 rounds
Dressler et al[94] (2010)	1 RBC, 1 plasma, 1 RDP	Repeat package 1	Repeat package 1	<3 kg, rFVIIa and cryo are at physician's discretion
	2 RBC, 2 plasma, 2 RDP	Repeat package 1	Repeat package 1	3–20 kg, rFVIIa and cryo are at physician's discretion
	4 RBC, 4 plasma, 4 RDP	Repeat package 1	Repeat package 1	21–40 kg, rFVIIa and cryo are at physician's discretion
	6 RBC, 6 plasma, 6 RDP	Repeat package 1	Repeat package 1	>40 kg, rFVIIa and cryo are at physician's discretion
Pickett and Tripi[95] (2011)	6 RBC, 3 FFP, 5 RDP	5 RBC, 3 FFP, 5 RDP	5 RBC, 2 FFP, 5 RDP, 10U cryo	
Chidester et al[96] (2012)	1 RBC, 1 FFP, 1 RDP	Repeat package 1	Repeat package 1	rFVIIa is at physician's discretion
Hendrickson et al[97] (2012)	1/2 RBC, 1/2 plasma	1/2 RBC, 1/2 plasma, 1/2 SDP	1/2 RBC, 1/2 plasma, 1 U cryo	Neonate (1–5 kg), 1 dose of rFVIIa at physician's discretion
	1 RBC, 1 plasma	1 RBC, 1 plasma, 1/2 SDP	1 RBC, 1 plasma, 2U cryo	Infant (6–10 kg), 1 dose of rFVIIa at physician's discretion
	2 RBC, 2 plasma	2 RBC, 2 plasma, 1 SDP	2 RBC, 2 plasma, 4U cryo	Younger child (11–25 kg), 1 dose of rFVIIa at physician's discretion
	3 RBC, 3 plasma	3 RBC, 3 plasma, 1 SDP	3 RBC, 3 plasma, 6U	Cryo older child (26–50 kg), 1 dose of rFVIIa at physician's discretion
	5 RBC, 5 plasma	5 RBC, 5 plasma, 1 SDP	5 RBC, 5 plasma, 8U cryo adolescent	>50 kg, 1 dose of rFVIIa at physician's discretion
Obstetric MTP				
Gutierrez et al[98] (2012)	6 RBCs, 4 AB TP or LP, 1 SDP	Repeat package 1	Repeat package 1	Consider rFVIIa as salvage treatment

Note: 1U cryo =1 individual unit (not 5- or 10-pooled unit) of cryoprecipitate.
Abbreviations: RBCs, red blood cells; RDP, random donor platelets; SDP, single donor apheresis platelets; FFP, fresh frozen plasma; TP, thawed plasma; LP, liquid plasma; TXA, tranexamic acid; rFVIIa, recombinant-activated factor VII.

Selection of available blood products

Red blood cells

To minimize blood product wastage, most blood banks aim to transfuse the oldest units first. However, the clinical impact of the RBC storage lesion has been heavily discussed and debated recently.[14] The clinical effect of storage lesions and transfusing older RBCs has been insightfully described by Wang et al in a meta-analysis article evaluating over 20 published studies, which suggested that transfusing older blood is significantly associated with an increased mortality risk. However, the significance of this association appears

Table 2 Summary of 2013 American College of Surgeons Trauma Quality Improvement Program (ACS-TQIP) Survey

Surveyed categories	Major findings (% of surveyed ACS-TQIP trauma centers)
Prehospital resuscitation	The most common blood products used were RBCs (28%) and plasma (10%) The most common intravenous hemostatic agent used is TXA (15%)
MTP activation triggers	The most common trigger used was hypotension (56%), defined as SBP of ≤100 mmHg (86%) Laboratory values were used infrequently (26%) to initiate MTP
Blood product use and policies	Plasma is available immediately or in <5 minutes (64%–72%). The most common plasma type used was thawed plasma or plasma frozen within 24 hours (78%) The most common plasma:RBC ratio in the first cooler was ≥1:2 (88%) The platelet:RBC ratio of ≥1:2 in the first blood pack was targeted (79%) The use of cryoprecipitate was integrated in the MTP policies (49%)
Hemostatic agent (at hospital)	The most common intravenous hemostatic agent used was TXA (50%)
Point of care coagulopathy evaluation	The integration of TEG in the MTP policies was low (18%)

Abbreviations: RBCs, red blood cells; TEG, thrombelastography; MTP, massive transfusion protocol; TXA, tranexamic acid; SBP, systolic blood pressure.

to vary with different patient populations.[15] McDaniel et al found that the age of RBCs transfused during non-trauma MTPs was not significantly different from during trauma MTPs. However, the age of transfused RBCs increased significantly when the patient was switched to type-specific RBCs, which inevitably happens during MTPs.[16] This is commonly practiced in many hospitals in order to preserve the Group O RhesusD (RhD) negative RBC inventory. In addition, the age of uncrossmatched Group O RBCs reserved for MTPs will vary due to hospital-specific RBC product management, thus further studies are needed in this area. Prospective randomized controlled trials (RCTs), including the ARIPI, ABLE, and RECESS trials, have shown that fresher RBCs do not significantly improve clinical outcomes or mortality in various clinical settings.[17–19] However, no prospective clinical trial has been published on the effect of RBC storage age on outcomes for MT patients.

Immune-mediated hemolysis is another clinical concern during the MTP. Due to the emergent need for blood products, routine pre-transfusion testing is bypassed and uncrossmatched Group O RhD negative RBCs are often given. This removal of safety assurances received from the antibody screen and product cross-matching leaves alloimmunized patients at increased risk for acute or delayed hemolysis.[20] In addition, residual plasma within Group O RBC units can accumulate when large quantities of Group O RBC units are transfused. This may theoretically lead to hemolysis due to ABO incompatibility based on retrospective evidence garnered from transfusing out-of-group platelets with minor ABO group incompatibility.[21,22] Thus, for A, B, or AB patients, it is safest to repeat the blood type, with particular consideration of the reverse type, before resuming transfusion of RBCs of the patient's own blood group.

Plasma

Circulating coagulation factors have variable half-lives and are homeostatically maintained. During massive hemorrhage, the acute nature of significant blood volume loss could lead to uncompensated coagulopathy. Therefore, early transfusion of plasma-containing physiologic coagulation factors intuitively should reverse this condition. Until recently, universal Group AB plasma has been the standard product used during MT when the patient's blood group is initially unknown. Since Group AB donors comprise only approximately 4% of all eligible US blood donors, and the availability of Group AB plasma donors has been further reduced by the transfusion-related acute lung injury (TRALI) mitigation strategies, Group AB plasma and platelet products remain scarce resources. To resolve this dilemma, the use of Group A plasma with low titer anti-B agglutinin has been considered as a practical alternative to Group AB plasma. Group A US donors are approximately ten times more abundant than AB donors.[23] Zielinski et al evaluated the clinical impact of using universal untitered Group A plasma transfusion and found that approximately 14% of study subjects received incompatible plasma but no significant adverse events occurred. Notably, this practice reduced the use of AB plasma by more than 95%.[24] Another retrospective study by Chhibber et al examined the outcomes associated with the use of Group A plasma versus Group AB plasma in an emergency setting. Of the 23 patients with blood Group B or AB, no hemolytic or other adverse reactions were detected.[25] Thus, transfusing low-titer A or even untested Group A plasma is a practical approach in MT practice.[26] On the contrary, neither low-titer Group A or untitered Group A plasma is considered equivalent to Group AB plasma during routine plasma transfusion practice.

There are multiple plasma products available in the blood bank (Table 3). The selection of the product is determined by timeliness of product availability and the coagulation factor content. Thawing large amounts of frozen plasma during an MTP presents a formidable logistical challenge to deliver the plasma products within 5–10 minutes of the

Table 3 Emergency plasma products available for massive transfusion

Plasma type	Clinical use (country)	Thawing time	Donor exposure	Universal use?	Product expiration USA (hours)
Fresh frozen plasma (thawed)	Worldwide	30–45 minutes	1	No	24 at 1°C–6°C
Thawed plasma	USA	No modification	1	No	120 at 1°C–6°C
Liquid plasma	USA	No modification	1	No	624 at 1°C–6°C
Lyophilized plasma					
LyoPlasN®	Germany	Bedside reconstitution	1	No	Immediate use
INTERCEPT Lyoplasma®	France	Bedside reconstitution	11	Yes	Immediate use
Pathogen-inactivated plasma					
Amotosalen (Intercept®)	Multiple	30–45 minutes	1	No	24 at 1°C–6°C
Solvent detergent (Octaplas®)	Multiple	30–45 minutes	1,000–1,500	No	24 at 1°C–6°C 8 at 20°C–25°C

request. In the US after fresh frozen plasma or plasma frozen within 24 hours is thawed and stored for 24 hours, it can be relabeled as thawed plasma (TP) with up to five more days of shelf life. Therefore, TP has gained wide acceptance for MTP use. An observational study evaluating the implementation of TP in an emergency transfusion protocol demonstrated a significant reduction for plasma delivery time, overall blood transfusion volume, and 24-hour and 30-day mortality.[27] TP has relatively less factor V and factor VIII than fresh frozen plasma and plasma frozen within 24 hours. Liquid plasma (LP) is plasma recovered within 5 days of expiration from a WB product (never frozen); therefore, it has a shelf life of 26 days from the day of collection. In vitro studies have shown that LP, when stored at 1°C–6°C for up to 26 days, appears to provide similar hemostatic properties to TP as assessed by thrombelastography (TEG) and inhibition of vascular endothelial cell permeability by the endothelial monolayer assay.[28] Goodnough et al reported that Group AB LP may be an acceptable alternative plasma product for trauma patients with unknown blood groups.[29] In comparison to traditional plasma products, lyophilized plasma is logistically more convenient to use during an emergency situation. In Germany, LyoPlas N is a single donor-derived product that can be stored at room temperature up to 15 months and is transfusion-related acute lung injury mitigation strategy compliant. While the single donor source reduces the risk of infection compared to pooled products, the product requires blood type-specific transfusion. A counterpart in France is branded INTERCEPT Lyoplasma. In contrast, this is a pooled, leukoreduced, pathogen-inactivated plasma product pooled from up to eleven donors. Lyoplasma can be stored at room temperature for up to 2 years and can be administered without ABO restriction. While these products are not yet clinically available worldwide, they are currently being evaluated in clinical trials.

Platelets

After collection from blood donors, platelets are typically stored between 20°C and 24°C with constant agitation for up to 5 days. In vitro and animal model-based studies have shown that refrigerated platelets have a shortened half-life in circulation.[30,31] While refrigeration (1°C–6°C) is associated with decreased platelet viability and post-infusion increments, cold platelets have been shown to more readily aggregate in vitro and to have a better metabolic profile.[32,33] During emergency resuscitation, the clinical emphasis often weighs more in favor of achieving rapid hemostasis rather than a durable increase in platelet count. Therefore, it has been suggested that refrigerated platelets dedicated for emergency transfusion may have clinical benefits.

Whole blood

In MT, blood component therapy attempts to recapitulate the qualities of WB; thus, the direct use of WB for bleeding trauma patients in a civilian setting has gained increasing attention. A platelet-sparing leukoreduction filter (ImuFlex, Terumo BCT, Lakewood, CO) system was recently approved by the FDA for WB processing. A single institution RCT evaluated the 24-hour transfusion volume in trauma patients receiving either WB or blood component therapy. While WB transfusion did not significantly reduce the transfusion volume in all patients, a portion of the trauma patients transfused with WB did receive significantly less blood volume.[34] There are ongoing clinical trials to examine the effects of WB transfusion in emergency settings. The major hurdle preventing the widespread use of platelet-sparing WB products is the lack of consensus on the optimal storage condition. An in vitro functional analysis on stored pathogen-inactivated WB treated with riboflavin and ultraviolet light revealed that a colder storage temperature (4°C) significantly preserved the hemostatic properties and

platelet function.[35] Another major limitation to the use of WB is the requirement for type-specific blood, as the patient blood type is frequently unknown during the early phase of resuscitation. Although WB appears to be a promising practice during MT, more practice optimization is needed prior to its wide acceptance.

Hemostatic therapies

The use of lyophilized factor concentrates and pharmacologic agents during MT has gained popularity as they can be stored and administered at the bedside to avoid time delays due to product processing and issuing. In addition, this allows the use of target-specific treatment rather than the broad and non-specific use of plasma to attempt to correct all coagulopathies. Three factor concentrates have been used in MT: prothrombin complex concentrates (PCCs), recombinant-activated factor VII, and fibrinogen concentrate.

Recombinant-activated factor VII (rFVIIa) and PCCs

Two main coagulation events determine the success of rapid and sustained clot formation: thrombin generation and fibrin formation. With rapid activation of thrombin in the presence of adequate fibrinogen and platelets, the early use of rFVIIa was associated with less blood product usage and lower mortality in military patients requiring MT.[36–38] A recent meta-analysis on the use of rFVIIa, in both military and civilian populations, for the prevention and treatment of hemorrhage demonstrated favorable trends in reducing blood product usage and mortality; however, there is a concurrent trend of increased thromboembolic adverse outcomes with rFVIIa.[39] Therefore, rFVIIa is not recommended for routine use during MT practices.

The use of 3- or 4-factor PCCs in a MT setting is observed due to its rapid availability and potent/rapid restoration of key vitamin K-dependent clotting factors in a concentrated, low volume dose. PCCs are not available or approved for use in a MT setting in all countries. However, the use of PCCs in dilutional coagulopathy and other clinical settings has been published to show significant hemostatic efficacy. In parallel, PCCs may carry potential enhanced risk of thrombosis in subsets of MT patients due to patients' increased circulating tissue factor and decreased plasma or endothelial anticoagulant activity.[40] With the lack of safety evidence, European guidelines do not endorse the use of PCC in a MT setting.[11] Collectively, these hemostatic agents are potent drugs with a risk of thrombosis; therefore, the risk-to-benefit ratio should be carefully considered in an MT setting.

Fibrinogen concentrate

Fibrinogen is a coagulation factor with a large molecular weight and a long half-life. When significant intravascular loss due to prolonged bleeding occurs, its recovery will be delayed and can rapidly become clinically significant.[41] Worldwide, cryoprecipitate remains the most common blood product used to replace fibrinogen and contains approximately 200–250 mg of fibrinogen per unit. In addition to the time delay from thawing the cryoprecipitate, the thawed product expires within 6 hours in most countries. This leads to delayed availability and increased product wastage. Furthermore, cryoprecipitate is a pooled product, but not pathogen inactivated. While fibrinogen concentrate was originally developed and approved to treat congenital afibrinogenemia, many in vitro and animal models have shown that fibrinogen concentrate can strengthen clot firmness and achieve early hemostasis in the presence of thrombocytopenia and dilutional coagulopathy.[42,43] A retrospective study correlating the fibrinogen level with mortality in critically injured patients revealed that fibrinogen levels less than 180 mg dL^{-1} were significantly associated with higher in-hospital death.[44] Fibrinogen replacement has been shown to hasten clinical hemostasis in various bleeding patient populations, including cardiovascular surgery, postpartum hemorrhage, and orthopedic surgery.[45–47] European guidelines recommend the initiation of fibrinogen replacement by fibrinogen concentrate when the plasma fibrinogen level falls below 1.5 g L^{-1}.[11] Holcomb et al have shown that fibrinogen replacement via cryoprecipitate is often delayed and overlooked during an MTP;[48] therefore, the use of fibrinogen concentrate may be well justified in an emergency setting to augment clot firmness and achieve better hemostasis. The cost of fibrinogen concentrate is much greater than cryoprecipitate in some countries.

Tranexamic acid

Antifibrinolytics, such as aminocaproic acid or tranexamic acid (TXA), inhibit the formation of plasmin; plasmin breaks down the fibrin-based clot. Therefore, they are used to improve the durability and firmness of the clot in order to enhance clinical hemostasis. Antifibrinolytic agents have been shown to be clinically beneficial in achieving hemostasis and reducing MT in exsanguinating trauma patients, especially after enhanced fibrinolytic activity has been detected.[49] Several published meta-analyses have demonstrated the efficacy and safety of TXA for bleeding patients in various surgical settings.[50–55] The largest prospective RCT utilizing antifibrinolytics is the Clinical Randomization of an Antifibrinolytic in Significant Hemor-

rhage 2 (CRASH-2) trial, a multicenter study that evaluated more than 10,000 trauma patients. The data analyses revealed that timely administration of TXA (within 3 hours of injury) was associated with a modest but highly significant reduction in both overall and bleeding-related mortalities, but not in MOF or head injury. In addition, there was no significant difference between the TXA and placebo groups in blood transfusion requirements or length of hospital stay.[56,57] As the effect of TXA on isolated traumatic brain injury was not well characterized in the CRASH-2 study, the CRASH-3 trial is now underway to determined optimal use of TXA in this patient population.[58] The first prospective RCT on the effectiveness of high-dose TXA (4 g loading dose with 1 g h^{-1} over 6 hours) in women with postpartum hemorrhage was conducted in France. In the 144 subjects evaluated, TXA significantly reduced blood loss and transfusions.[59] Currently, the World Maternal Antifibrinolytic Trial was established to examine the effect of TXA in women with postpartum hemorrhage on mortality and other adverse events.[60]

Evaluation of coagulopathy during MTP activation

Viscoelastic testing

Currently, central laboratory-based hemostatic evaluations (eg, prothrombin time [PT], international normalized ratio [INR], activated partial thromboplastin time, fibrinogen level/activity, and platelet count) are most commonly used in all clinical settings, including trauma. However, many of these tests are not designed for diagnosis of coagulopathy or to guide hemostatic therapy.[61] In addition, they may not have adequate turn-around-time (TAT) to guide coagulation factor or platelet replacement during the fast pace of a MT. Thus, an accurate and rapid POC device to evaluate a patient's pre- and post-transfusion clotting capacity would be a great asset to direct blood transfusion and the use of hemostatic agents. Currently, there are two POC assays to evaluate real-time global coagulation function using viscoelastic methodology: thrombelastography (TEG®) and rotational thromboelastometry (ROTEM®). Viscoelastic testing evaluates the four main components of hemostasis: clot initiation, clotting amplification, clot firmness, and the dynamics of fibrinolysis (Figure 1). To date, there are more than 30 clinical trials showing that viscoelastic testing can reduce blood transfusion and improve clinical outcomes in patients with surgery- and trauma-related massive hemorrhage. Tapia et al have shown that MT guided by TEG® is superior in resuscitating patients with penetrating trauma when compared to standard MT practice.[62] Notably, a recent prospective RCT

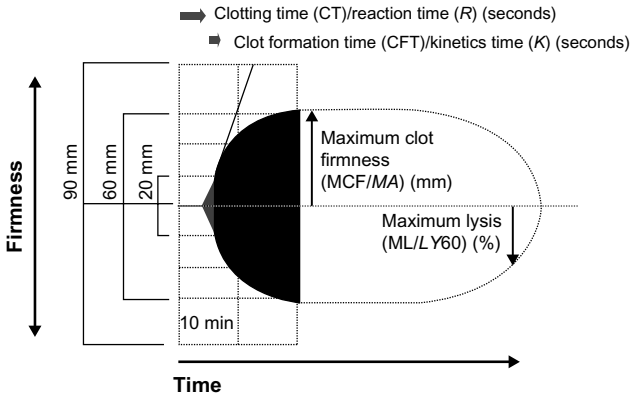

Figure 1 Parameters of ROTEM and TEG.
Abbreviations: MA, maximum amplitude; LY, clot lysis; TEG, thrombelastography; ROTEM, rotational thromboelastometry.

showed that FIBTEM A5 (the clot firmness in a functional fibrinogen test of ROTEM® at 5 minutes) is an independent predictor for greater than 2.5 L of blood loss during postpartum hemorrhage.[46] Similarly, Meyer et al demonstrated that ROTEM® clot firmness at 10 minutes was helpful in predicting who would require MT in a trauma population.[63] Thus, not only can viscoelastic testing provide real-time coagulation analysis, it also has the potential to predict large blood loss and may be a useful MTP prediction tool. In addition, it has the ability to guide early, targeted therapy and allows the monitoring and early treatment of hyperfibrinolysis. Many hospitals have incorporated immediate viscoelastic testing within an hour of admission and after each MTP cooler until bleeding is controlled surgically to enhance practice during trauma MTPs. With ROTEM®/TEG® monitoring, hemostatic therapy is guided using a combination of plasma (or PCCs in countries where they are available), platelets, fibrinogen (fibrinogen concentrate or cryoprecipitate), and antifibrinolytic agents (TXA or aminocaproic acid). This approach is most effective when transfusion algorithms incorporating POC testing have been created and practitioners have been appropriately trained on the protocols. Additional studies evaluating the utilization of viscoelastic testing in non-trauma MTPs and the ideal location for testing POC/blood bank/central laboratory would be worthwhile.

POC WB prothrombin time assay

Laboratory-based plasma PT and INR are simple tests designed to monitor warfarin effect, but they have been widely adopted to evaluate hemostasis and assess general bleeding risk. The use of PT/INR has been integrated into several predictive algorithms for MTP activation due to its simple procedure, low cost, and transfusion predictability;[64–66] however, its significant delay in TAT (~30–60 minutes)

makes it less practical to direct timely therapeutic decisions during patient resuscitation with blood products. With the availability of a POC PT/INR assay using WB, the results of the PT/INR can be rapidly available at the patient's bedside during MT. Two observational studies have compared the performance of POC PT/INR assay against either plasma PT/INR or TEG in the setting of trauma.[67,68] The investigators in one study concluded that POC PT/INR assay has comparable accuracy to the laboratory-based PT/INR assay, and the ability to predict blood transfusion requirements.[67] In addition, they reported a significant reduction of TAT and laboratory costs (including reagents and labor). However, performance is specific to each individual POC device and larger studies examining various commonly used POC PT/INR devices in various clinical settings and types of coagulopathy will be required to gain full endorsement for this testing option.

Designing an optimal MTP

Predicting MTP utilization

As trauma patients requiring MT often die within 6 hours of medical resuscitation efforts,[69,70] a reliable formula to predict MTP usage would be of great value. There are several published algorithms to predict the need for trauma-MTP in both civilian and military settings (Table 4).[64–66,71–78] For example, Assessment of Blood Consumption scoring system developed by Cotton et al is a non-weighted scoring system that was validated at multiple Level I trauma centers. It is a simple system, relying on only a few rapidly obtainable clinical parameters, yet its performance was robust.[76,79] Most recently, the shock index (SI), which is the ratio of heart rate to systolic blood pressure, was developed as a simple predictor to evaluate trauma outcomes.[80,81] Sohn et al have evaluated the use of SI in the setting of postpartum hemorrhage and found that SI can also independently predict the use of MTP in that setting.[82] Other weighted scoring systems incorporating laboratory values, such as the Trauma-Associated Severe Hemorrhage and the Prince of Wales Hospital scores also appear to be reliable predictive tools for MTP utilization.[83,84] Furthermore, POC instrument-based predictive algorithms have gained a great deal of interest due to simplicity, faster TAT, and less inter-observer variability.[75,77] There are several published comparative studies to determine the ideal predictive system; however, the results vary due to different validation cohorts and study design biases. These systems have not been studied extensively in either the non-trauma MTP or pediatric MTP setting. A systematic comparison of these algorithms is needed to generate the best consensus practice to predict the need for MTP.

Table 4 MT prediction algorithms

Algorithms	Prediction parameters
Trauma-associated severe hemorrhage (TASH)	Hgb, base excess, systolic BP, HR, FAST (+), male sex, pelvic and femur fractures
Prince of Wales Hospital (PWH)	Hgb, systolic BP, GCS, HR, FAST (+), base deficit, pelvic fracture
Assessment of blood consumption (ABC)	Penetrating trauma, BP, HR, FAST (+)
Trauma-induced Coagulopathy Clinical Score (TICCS)	Injury severity, BP, extent of injury
Automated software-derived prediction (Mackenzie et al[77])	HR, SpO_2, wave form analysis (pulse oximeter values)
Traumatic Bleeding Severity Score (TBSS)	Age, sex, systolic BP, FAST (+), pelvic fracture, lactate
Leemann et al[75]	ROTEM (A5, A10, Maximum Clot Firmness)
Olaussen et al[81]	Shock Index (HR, systolic BP)
Barbosa et al[78]	GCS, pH, HR, age, Injury Severity Score, 6-hour RBC transfusion requirement
Huang et al[64]	Pre-operative INR
Hsu et al[65]	INR, base deficit, hemoperitoneum at laparotomy
Callcut et al[66]	INR, systolic BP, Hgb, base deficit, FAST (+), HR, penetrating trauma

Abbreviations: Hgb, hemoglobin; BP, blood pressure; HR, heart rate; FAST, Focused Assessment with Sonography in Trauma; GCS, Glascow Coma Scale; SpO_2, peripheral blood oxygen saturation; INR, international normalized ratio.

Logistical and safety considerations

Many MTPs begin with blood from a remote refrigerator in the emergency department or trauma bay. Often these refrigerators are stocked with Group O RBCs and occasionally TP in large trauma centers. Additional blood can be obtained from the blood bank in coolers. The amount and type of blood products per cooler varies depending on institutional preference and the blood bank inventory (see examples in Table 1).[85–98] A prolonged MTP (more than 10–20 blood products) can quickly exhaust the supply of universal blood products, including Group O RBCs. Many blood banks use a rule of greater than 10 units issued before switching to RhD positive (for RhD negative patients) or antigen untested RBCs for patients with atypical red cell alloantibodies, but occasionally if sufficient RBC units are not available, the switch must occur earlier. During an MTP, time-consuming blood component processing, such as irradiation or cell washing, is not feasible.

Although MT can be life-saving, it carries inherent risk and harm that may occur when it is utilized inappropriately (Table 5). As blood products are needed emergently during an MTP, routine pre-transfusion testing is bypassed. Uncrossmatched Group O RhD negative RBCs, Group AB

Table 5 Adverse complications associated with massive transfusion

Acute	Delayed
TRALI	Hemolysis
TACO	TRIM
Citrate toxicity/hypocalcemia	Transfusion-associated GvHD
Hypothermia	Microchimerism
Allergic reaction	Transfusion-transmitted infection
Hyperkalemia	Posttransfusion purpura
Hemodilution (pediatric)	
Dilutional coagulopathy/ thrombocytopenia	
Febrile non-hemolytic transfusion reaction	
Electrolyte and acid–base imbalance	
Infection	
Multiorgan failure	
Systemic inflammatory response syndrome	

Abbreviations: TRALI, transfusion-related acute lung injury; TACO, transfusion-associated fluid overload; TRIM, transfusion-related immunomodulation; GvHD, graft versus host disease.

or low titer Group A plasma, and Group AB or A platelets are conventionally used. These blood products may result in various adverse transfusion events, including hemolysis, alloimmunization, hypothermia, citrate toxicity, and hyperkalemia. The switch from Group O RhD negative RBCs to the patient's specific blood type should occur as soon as possible after the patient's blood type has been confirmed on two independent specimens.

Timely MTP activation and deactivation

MT is a resource-intensive process. As exsanguination-associated death usually happens during the first few hours of admission, this resuscitative effort needs to occur within minutes. For many trauma centers, the time to issue the first MTP cooler is usually within 5–10 minutes from protocol activation. Given the need for rapid TAT and large amounts of different blood products, the blood bank often requires a dedicated team to coordinate blood preparation for the duration of MTP activation. Predictably, the rapid mobilization of large amounts of blood products in response to highly unpredictable clinical needs often results in inefficient use and blood product wastage. To ensure that an MTP is legitimately activated and to reduce potential unnecessary blood transfusion, transfusion medicine specialists are often consulted prior to commencing with MTP blood preparation, especially for non-trauma cases. In parallel, the clinical physicians should be educated on the appropriate use of MTPs. At the bedside, the clinician who activates the MTP should serve as the liaison to inform the blood bank about the need for continuing transfusion support or deactivation of the MTP. Timely deactivation of MTPs not only reduces wastage, but also may prevent unnecessary adverse events associated with MTP. A formal retrospective process involving the blood bank and the clinical teams to evaluate the efficiency and performance of each MTP and the associated outcomes can be beneficial to continuously improve the MTP.

Appropriate product ratios during MT

Without the universal availability of POC testing, an optimized transfusion strategy with appropriate blood component selection is critical. Several published retrospective studies have shown that a higher plasma to RBC ratio in MT is associated with better survival in patients with traumatic injuries.[99] Since 2007, there has been a rather accelerated shift in MT practice to utilize a higher plasma:platelet:RBC ratio.[100,101] However, the retrospective studies are thought to be flawed due to survival bias (patients who survive longer are more likely to receive plasma). Holcomb et al conducted a prospective observational study on the effect of a higher plasma:RBC ratio on in-hospital mortality. Over 900 eligible trauma patients receiving more than three

Table 6 Summary of findings from PROMMTT and PROPPR studies

	PROMMTT[102]	PROPPR[103]
Year	2013	2015
Source	JAMA surgery	JAMA
Study design	Prospective observational	Randomized control trial
Intervention	Plasma:RBCs (1:1)	Plasma:platelets:RBCs (1:1:1); n=338
Control	Plasma:RBCs (1:2)	Plasma:platelets:RBCs (1:1:2); n=342
Cohort size (n)	905	680
Generalizability	Multicenter study	Multicenter study
Follow-up	24-hour and 30-day	24-hour and 30-day
Primary endpoint	In-hospital mortality	24-hour and 30-day mortality
Outcomes	Higher plasma:RBC ratio decreases 6-hour mortality in patients who received >3 blood products; however, no association found after 24 hours of survival	No significant difference in 24-hour and 30-day mortality or complications. 1:1:1 group achieved earlier hemostasis and had less mortality due to exsanguinations in 24 hours

Abbreviations: PROMMTT, Prospective Observational Multicenter Major Trauma Transfusion; PROPPR, Pragmatic, Randomized Optimal Platelet and Plasma Ratios.

RBCs unit were analyzed and found that less than 1 plasma for every 2 RBC products is associated with a three- to four-fold higher death risk within 6 hours of admission.[102] However, the transfused plasma:RBC ratio significantly varied within the analyzed cohort. To control for this potentially clinically significant variable, the Pragmatic, Randomized Optimal Platelet and Plasma Ratios study was conducted to examine the effect of 1:1:1 versus 1:1:2 plasma:platelet:RBC ratio on 24-hour and 30-day all-cause mortality.[103] The study showed that while there was no difference in the examined all-cause mortality, there was earlier hemostasis, lower transfusion requirements, and less death due to exsanguination at 24 hours in the 1:1:1 ratio group (Table 6). While there are still study limitations and biases due to the complex nature of conducting a multicenter RCT in a trauma setting, the Pragmatic, Randomized Optimal Platelet and Plasma Ratios study concluded that the higher plasma:platelet:RBC ratio appeared to be effective in reducing mortality. A higher fibrinogen-to-RBC ratio is also associated with improved survival during MT.[104] More controlled investigations are still required to establish optimal blood product ratios.

Summary

In conclusion, the best practice for MT includes an established institutional definition of MT, an accurate method for predicting which patients will require MT so therapy can be promptly initiated and over-utilization can be avoided, and finally, an established MT protocol with a clear plan for activation and use of appropriate blood products to maintain hemostasis.[105] This can be achieved either by goal-directed therapy with POC testing or, when point-of-care testing is not available, fixed ratios of blood products approximating a ratio of 1:1:1, with early initiation of fibrinogen replacement. Adherence to the established protocol is critical to extract the full clinical benefit of an MTP for treating either trauma or non-trauma patients.

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