Review Article

Massive transfusion: a review

Sarah A. Moore[1], **Jay S. Raval**[2]

[1]Division of Acute Care Surgery, Department of Surgery, University of New Mexico, Albuquerque, NM, USA; [2]Section of Transfusion Medicine and Therapeutic Pathology, Department of Pathology, University of New Mexico, Albuquerque, NM, USA

Contributions: (I) Conception and design: Both authors; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: Both authors; (V) Data analysis and interpretation: Both authors; (VI) Manuscript writing: Both authors; (VII) Final approval of manuscript: Both authors.

Correspondence to: Jay S. Raval, MD. Director, Section of Transfusion Medicine and Therapeutic Pathology, Department of Pathology, University of New Mexico, MSC08 4640, Albuquerque, NM 87131, USA. Email: jraval@salud.unm.edu.

Abstract: Patients with massive hemorrhage require a nuanced resuscitation to maintain circulation and achieve hemostasis. Massive transfusion (MT) forms the central core of this resuscitation and involves the rapid administration of large volumes of blood products including red blood cells (RBCs), plasma, platelets (PLT), cryoprecipitate (CRYO), and whole blood (WB). Referred to as hemostatic resuscitation, this transfusion strategy of providing plasma- and platelet-containing blood products in addition to RBCs has been recommended to prevent hemodilution and to restore coagulation function closer to normal, potentially providing better control of hemorrhage and improving outcomes. As a result, many institutions have implemented MT protocols (MTPs) designed to efficiently deliver pre-determined amounts of RBCs, plasma/CRYO, and PLT. A multidisciplinary team is necessary to ensure safe and efficient MT activation, allocation, documentation, and transfusion; necessary representatives include members from units such as surgery, medicine, anesthesiology, and obstetrics, the blood bank, and hospital quality committee to name but a few. This review article will discuss the history of MT, provide various definitions for massive hemorrhage and MT, explain the pathophysiology of the acutely bleeding patient, highlight balanced hemostatic resuscitation and its critical elements in various patient populations, examine various clinical tools to predict those who may require MT, elucidate blood bank and quality activities that support MT, assess different adjunctive therapies, inform about possible complications of MT, and speculate about the possible future evolutions in MT.

Keywords: Massive transfusion (MT); trauma; hemorrhage; hemostatic resuscitation

Received: 24 January 2022; Accepted: 03 March 2022; Published: 30 June 2022.
doi: 10.21037/aob-22-3
View this article at: https://dx.doi.org/10.21037/aob-22-3

Evolution of massive transfusion (MT)

Over the last century, significant advancement in MT has allowed for the development of modern MT protocols (MTPs). Like in many areas in trauma, military conflict has shaped much of the practice of MT. During World War I, techniques for formal blood banking were established, and were recognized as one of the most important medical advances of the time (1). Whole blood (WB) was freshly prepared and immediately transfused. When World War II began, these formal blood-banking resources were not available and thus freeze-dried plasma was the primary military transfusion product, with poorer outcomes documented. By 1944–1945, the American Red Cross had established a robust blood banking program and shipped 2,000 units of WB per day to the European and Pacific theaters (1,2). Fractionation techniques were developed after World War II, allowing WB to be separated into packed red blood cells (PRBCs or RBCs), plasma, platelets (PLT), and cryoprecipitate (CRYO). Despite supporting evidence, it was thought that separating WB into components would both maximize the number of

available products and limit unnecessary transfusions, thus potentially limiting transfusion-related complications. As a result of this, WB fell out of civilian practice until a recent resurgence in interest and use (3).

One of the first literature references that describes a formalized MTP was in 1985, where a "Code Red" protocol is used to describe an initial "*massive crystalloid infusion*, *followed by rapid access to*, *and infusion of*, *blood*" (4). By 2006, a survey of major trauma centers across the world found that few centers had adopted a formal MTP. With several landmark trials touting the benefits of balanced resuscitation and the MTP use published over the subsequent few years, as well as the description and wide-spread adoption of the concept of damage control resuscitation, 85% of centers responding to a survey reported having a MTP by 2010 (5). By 2016, 98% of centers reported having an MTP (6). A range of contents within MTP and a variety of indications for activating it have been reported, with trauma being the single most common indication for activating MTP in adult and pediatric patients, but with non-trauma indications representing the majority of reasons for which MTP was activated (7).

Definitions of MT

The classic definition of MT was defined during the Vietnam War as the transfusion of 10 units of blood in a 24-hour period. However, multiple flaws have been identified with this definition, the most significant of which is the survival bias—patients must survive 24 hours to meet this definition, and thus the truly massively hemorrhaging patient who dies in the first several hours prior to meeting the 10-unit threshold is not captured. Additionally, this definition does not capture the intensity of resuscitation. Thus, two more modern scores, the critical administration threshold (CAT) (8) and resuscitation intensity (RI) (9), were developed to capture patients missed by the original MT definition. RI was developed by the Prospective Observational Multicenter Major Trauma Transfusion (PROMMTT) study investigators. This score encompasses all resuscitation fluid given to a patient within 30 minutes of arrival, with 1 L of crystalloid, 0.5 L of colloid, and 1 unit of PRBC, plasma, or apheresis PLT all counted as one unit. Patients who received 4 or greater units of resuscitation fluid have a 3-fold increase in mortality at 6 hours, and a 76% increased mortality at 24 hours (9). CAT defines a patient as "CAT-positive" if they receive 3 or more units of PRBC within any one-hour time frame during the first 24 hours after injury. CAT-positive patients have a 4-fold increase in overall mortality. Both RI and CAT have improved sensitivity and specificity for mortality compared to the classic MT definition of 10 units in 24 hours (10). With the increasing utilization of cold-stored WB in modern resuscitation, a WB MT score was recently proposed, defined as the sum of each unit of RBC plus three times each unit of WB, with a score threshold of 7 defining MT (11). WB MT patients had 6-fold higher mortality at 24 hours than patients who did not meet this threshold.

In situations where transfusion access is limited or unavailable, it may be more helpful to capture massively hemorrhaging patients by blood volume lost, rather than clinician response to hemorrhage. The Joint United Kingdom Blood Transfusion and Tissue Transplantation Services define major hemorrhage as loss of greater than one blood volume in 24 hours (>5 L in a 70 kg adult), >50% of total blood volume lost in >3 hours, or bleeding in excess of 150 mL/minute (12). However, given the limitations in estimating volume of blood lost, these definitions have somewhat limited utility.

Epidemiology

MT accounts for only a small proportion of blood products transfused. In acutely injured trauma patients, only 3% of US civilian patients and 7% of military patients require MT (13). However, once transfusion is required due to traumatic hemorrhage, a larger proportion of patients require MT. In one single-center study, 25% of trauma patients requiring transfusion required an MT (>10 units/24 hours). In another study of all transfusion episodes in Denmark and Sweden, only 5.3% of all transfusion episodes were MT (14). Most MT events are for non-traumatic causes of hemorrhage, with rates ranging from 58–90% depending on the population studied (7,15).

Pathophysiology of acute traumatic coagulopathy

The importance of a MTP is paramount in the prevention and treatment of trauma-induced coagulopathy (TIC). TIC describes the abnormal coagulation processes that occur after trauma. First described by Brohi in 2003, it was initially thought to be largely the result of iatrogenic administration of excessive crystalloid fluids and hypothermia (16). It is now better understood to be a complex, multifaceted state characterized by both hypo- and hyper-coagulability, with

pathophysiological mechanisms that involve the coagulation system, immune system, and endothelial system (17). It is accentuated by the development of the "lethal triad" of coagulopathy, hypothermia, and acidosis, described by Moore in 1996 (18). Despite decades of research, there is no standard definition of TIC. Early TIC, within the first several hours after injury, is generally characterized by hypo-coagulability and inability to achieve hemostasis. This occurs in approximately 25% of severely injured patients and has an associated mortality of 35–50% (19). Late TIC, which usually occurs greater than 24 hours after injury, is characterized by a hyper-coagulable state, with both macro-thrombosis such as venous thromboembolism, and microvascular thrombosis that can result in multiple organ failure.

Multiple mechanisms for the development of TIC have been described. With the description of a "cell-based" model of hemostasis by Hoffman and Monroe in 2001, a more robust understanding of the mechanisms of hemostasis beyond a cascade of clotting factors was achieved (20). This model describes three overlapping stages: (I) initiation, which occurs on a tissue-factor bearing cell; (II) amplification, where PLT and cofactors are activated to generate thrombin; and (III) propagation, when large amounts of thrombin are generated on the platelet surface. This model allowed for a better understanding of the multiple pathways that might contribute to TIC. The combination of tissue injury and tissue hypoperfusion are critical to activating this pathologic state. These initial insults result in activation of protein C, oxidative stress, hyperfibrinolysis, release of damage-associated molecular pattern molecules (DAMPs), endothelial dysfunction, platelet aggregation impairment, and other pathologic processes that all contribute to the development of TIC.

MT is a fundamental treatment strategy to mitigate the effects of TIC. Identifying patients at risk for TIC and who may require MT is vital. Clearly, iatrogenic exacerbation of TIC via an unbalanced resuscitation and excessive crystalloid administration is to be avoided, and MTPs to increase immediate access to blood products are essential to these efforts. In fact, hemodilution from fluid administration is associated with a dose-dependent increase in coagulopathy. Early transfusion of plasma has been shown to ameliorate traumatic endotheliopathy by stabilizing the endothelial glycocalyx (21). CRYO has also been demonstrated to have similar endothelial protective effects (21).

Prediction of need for MT

Given the importance of early identification for the need for MT, predicting which patients need a MT is of great interest. Attempts to use isolated variables to predict the need for MTP activation have been of mixed success. Clinical parameters such as heart rate (HR), systolic blood pressure (SBP), altered mental status, and penetrating trauma mechanism have all been shown to predict need for MT, as have lab values including base deficit, international normalized ratio (INR), hemoglobin (Hb), hematocrit (HCT), pH, and viscoelastic testing values (22). Need for uncrossmatched RBC transfusion in the emergency department also independently predicts need for MT, with a sensitivity of 80% and specificity of 55% (23). Clinicians often unconsciously take many of these variables into account when making the decision to activate MTP, and pattern recognition and experience generally influence clinicians to decide to activate MTP. During the PROMMTT study, attending trauma surgeons were asked to assess whether patients were likely to be massively transfused at 10 minutes after patient arrival, based on their clinical gestalt (24). The overall sensitivity of this clinician intuition was 66% and specificity was 64%. Given the relatively low accuracy, scoring systems that incorporate multiple data points have been developed to help predict need for MT (see *Table 1*).

Given the limitations of single data points and clinician gestalt, other scoring systems have been developed that attempt to balance accuracy with rapidity and ease of use. The ideal scoring system should have high sensitivity and specificity, be immediately able to be easily calculated based on clinical data, and should not be reliant on laboratory testing or imaging that may delay the ability to calculate scores.

The first scoring systems to be adopted are the trauma-associated severe hemorrhage (TASH) score, described in 2006 (26), and the McLaughlin score, described in 2008 (27). The TASH score incorporates 7 variables that are incorporated into a final score in a weighted fashion. The variables included are SBP (<100 mmHg =4 points, <120 mmHg =1 point), Hb (<7 g/dL =8 points, <9 g/dL =6 points, <10 g/dL =4 points, <11 g/dL =3 points, and <12 g/dL =2 points), intra-abdominal fluid (positive =3 points), complex long bone and/or pelvic fractures [abbreviated injury scale (AIS) 3 and 4 =3 points and AIS 5 =6 points], HR (>120 bpm =2 points), base excess (<10 mmol/L =4

Table 1 Scoring systems to predict need for MT

Score	Components	AUROC
Clinical gestalt (24)	Clinician judgement	0.620
SI (25)	SBP/HR	0.832
ABC (25)	Penetrating mechanism	0.859
	Positive FAST	
	SBP	
	HR	
TASH (26)	SBP	0.842
	Hb	
	Intra-abdominal fluid	
	Complex long bone/pelvic fracture	
	HR	
	Base excess	
	Gender	
McLaughlin (27)	HR	0.767
	SBP	
	pH	
	HCT	

MT, massive transfusion; AUROC, area under the receiver operator characteristic curve; SI, shock index; ABC, Assessment of Blood Consumption; TASH, trauma-associated severe hemorrhage; SBP, systolic blood pressure; HR, heart rate; FAST, Focused Assessment of Sonography in Trauma; Hb, hemoglobin; HCT, hematocrit.

points, <6 mmol/L =3 points, and <2 mmol/L =1 point), and gender (male =1 point), with a range of scores from 0 to 28. Scores are then translated into a risk of requiring MT using a logistic regression, $P = 1/[1 + \exp(4.9 - 0.3 \times TASH)]$; a score of 16 predicts a 50% chance of requiring MT. The area under the receiver operator characteristic curve (AUROC) has varied from 0.72 to 0.90 depending on the patient population studied (22). Given the complexity of calculation as well as reliance on laboratory and imaging data, the clinical utility of the TASH score is limited. The McLaughlin score, developed in a combat casualty population, incorporates 4 data points: HR >105 bpm, SBP <110 mmHg, pH <7.25, and HCT <32% (27). These variables are incorporated into the equation $\log[P/(1 - P)] = 1.576 + (0.825 \times SBP) + (0.826 \times HR) + (1.044 \times HCT) + (0.462 \times pH)$. Given the need for laboratory data and complex mathematical calculations, this scoring system also has not achieved widespread adoption.

The two scoring systems that have most recently achieved widespread adoption are the shock index (SI) and the Assessment of Blood Consumption (ABC) score. SI is calculated as HR divided by SBP. Benefits of SI are its ease of use due to simple math and readily available data points, as well as its applicability to non-trauma patient populations with massive hemorrhage. SI >1.0 has been found to correlate with mortality and other poor outcomes including degree of shock and left ventricular performance (28). In one study of trauma patients, the AUROC for SI ≥1.0 was 0.83 (25). The ABC score, like SI, is calculated using simple math and readily available data points (29). One point is assigned for the presence of 4 variables: HR ≥120 bpm, SBP ≤90 mmHg, penetrating mechanism, and positive Focused Assessment of Sonography in Trauma (FAST) exam. A score of 2 or greater has a sensitivity of 75% and a specificity of 86% for predicting MT, with AUROC of 0.842 in the initial development study, and 0.83 to 0.90 in a multicenter validation cohort (30).

Key elements of MTPs

Modern MTPs are developed and implemented by a multidisciplinary team of members, including blood banking services, pathology and transfusion medicine, acute care surgeons, emergency medicine physicians, intensivists, anesthesiologists, and ancillary staff, as well as quality improvement experts and others. Having multidisciplinary buy-in is critical to the success of implementing an MTP. Activation of the MTP occurs by the treating clinician, which may include prehospital providers in pre-defined circumstances (31). This activation prompts blood banking services to prepare and deliver pre-set packages of various blood components in a pre-determined sequence, until hemorrhage slows and laboratory testing allows for a more tailored resuscitation (32). Standardization of MTP helps provide earlier administration of blood products during the initial resuscitation phase, improves overall efficiency, decreases total blood product use, and decreases crystalloid infusion, all with a resultant substantial cost savings (33).

Maintaining a balanced resuscitation during MT is critical. The Pragmatic Randomized Optimal Platelet and Plasma Ratios (PROPPR) study was a multicenter randomized trial investigating a PRBC:plasma:PLT ratio of either 1:1:1 or 2:1:1 (34). The investigators found that early resuscitation with a 1:1:1 ratio resulted in greater

rates of achieving hemostasis and fewer deaths due to exsanguination at 24 hours. A post-hoc analysis of the PROPPR database demonstrated that for every minute of delay of MTP product cooler arrival, mortality increased by 5% (35). When evaluating trauma patients who received an ultra-MT (≥20 units of RBC in 24 hours), transfusion of PRBC/plasma ≥1.5:1 or PRBC/PLT ≥1.5:1 was significantly associated with mortality (36).

One means of achieving a balanced resuscitation is with the use of WB instead of component therapy. The combination of plasma, PLT and PRBC components in a 1:1:1 ratio is estimated to result in a HCT of 25%, coagulation factor activity of 62%, platelet concentration of 50×10^9/L, and fibrinogen concentration of 75 mg/dL. In comparison, a unit of fresh WB has a HCT of 45%, 100% activity of all coagulation factors, platelet concentration of 200×10^9/L, and fibrinogen concentration of 150 mg/dL (37). Military combat experience has demonstrated that fresh WB via a "walking blood bank" is associated with improvements in mortality at 24 hours and 30 days post-injury (38). However, feasibility of a civilian warm fresh WB program is limited (although it has been used safely and effectively in austere settings) (39), thus prompting the use of uncrossmatched cold-stored low-titer group O WB (LTOWB). LTOWB has been demonstrated to be safe, with the benefit of ease of providing an inherent balanced resuscitation, allowing increased shelf-life of a platelet-containing product, and decreasing exposure to multiple donors (40). With a change in the AABB standards for the transfusion of WB such that it is no longer required to be ABO-identical to the recipient, more trauma centers are adopting the use of LTOWB over recent years (41,42). Civilian data has been mixed regarding improved outcomes with the use of LTOWB, with some studies finding improvements in trauma bay survival, 24-hour and 28-day survival, and others finding no mortality benefit (43-45). Further multicenter trials hope to help elucidate the true benefit of LTOWB in the civilian setting (46).

Blood bank logistics

Blood banks require an initial type-and-screen as well as an additional verification step to confirm ABO/D grouping for a specific patient before crossmatch-compatible RBCs may be issued (47). In trauma patients receiving hemostatic resuscitation, group O RBC products, group A or AB plasma products, and any group platelet products are typically issued to minimize the risk of ABO mismatch-mediated hemolytic transfusion reactions while still providing life-saving hemotherapy until required testing is completed so that ABO group-specific products may be issued. To optimize inventory management of these universal blood components for massively bleeding patients, early collection of type-and-screen samples is necessary. While transfusion of ABO incompatible plasma from any blood component to these civilian trauma patients may cause concern for increased adverse events, two retrospective studies have shown that this is not the case. In the safety of the use of group A plasma in trauma (STAT) study, it was shown that those 354 group B or AB trauma patients receiving group A plasma during initial resuscitation was not associated with increased in-hospital mortality, early mortality, or hospital length of stay versus those 809 group A patients that received group A plasma (48). Similarly, in an analysis of 2,618 trauma patients, the 1,282 who received any ABO-incompatible plasma were not found to have different 6-hour, 24-hour, or 30-day mortalities from those 1,336 patients who received no ABO-incompatible plasma (49). Thus, ABO-incompatible plasma does not appear to be associated with increased adverse events during the early resuscitation of trauma patients. Furthermore, in a retrospective multicenter study of 695 trauma patients, it was demonstrated that transfusion of up to 10 units of uncrossmatched type O PRBCs or LTOWB did not usually interfere with subsequent determinations of approximately 97% of recipients' ABO typings (50). This mollified concern for the potential of mistyping non-group O trauma patients after transfusion of uncrossmatched group O RBC-containing products.

Other blood bank considerations exist that also warrant comment. Blood banks typically have a "first-in-first-out" inventory policy for most patients, which could potentially result in the delivery of large volumes of older RBCs to massively hemorrhaging trauma patients (51,52). However, it has been shown that older RBCs are not preferentially issued to patients for whom emergency release or MTP have been requested (53). Furthermore, special manipulations or testing of blood components, such as irradiation, hemoglobin S (HbS) negativity, and washing, are often waived in the setting of massive hemorrhage and MTP activation due to the inherent delays associated with providing these unique products. Importantly, it has been shown that activation of an MTP to request massive quantities of blood products results in significantly faster issuing with less variability compared to ad hoc ordering of blood components (54), though overactivation of the MTP

was noted as a potential concern for over 50% of non-trauma patients. Expeditious delivery of blood products during massive hemorrhage, particularly trauma, has been shown to be associated with decreased mortality (35). Lastly, CRYO is being increasingly used in settings of massive hemorrhage, though rapid availability and wastage are concerns given its need to be thawed and subsequent expiration in a 4–6 hours.

Quality evaluation and improvement

Monitoring quality metrics and adherence with MTPs is a critical part of ensuring the success of the MTP process. One study evaluated compliance with MTP at a single institution and found that compliance with MTP had a significant survival benefit, with full compliance resulting in an 86.7% survival versus noncompliance resulting in 45.0% survival (55). Another study evaluated adherence with MTP and found that non-compliance was as high as 47% (56). They then divided compliance in to low, medium, and high compliance, and found that while the groups had similar patterns of injury and depth of shock, mortality increased from 10% to 50% to 62% as compliance with the protocol decreased from high to moderate to low compliance (56). Given this association, performance improvement (PI) by a multidisciplinary PI committee is vital. Suggested metrics to evaluate for compliance include timing of MTP activation, timely type and screen samples being sent to the lab, timeliness of blood product release from the blood bank, ratios of product administration, appropriate storage of unused blood products, appropriate discontinuation of the MTP when active exsanguination has ceased (57), and product wastage analysis (54,58). These metrics and any other concerns identified during the review of patients requiring MTP, should be evaluated on a regular basis by all stakeholders to ensure the efficient and appropriate functionality of the MTP.

Special patient populations

The vast majority of the research on the utility of MTP has focused on patients with exsanguination secondary to traumatic injury. Depending on the location studied, however, the majority of MT events are likely secondary to non-traumatic hemorrhage. In one study at a large, urban, academic medical center in the US, over 90% of MT events were secondary to non-traumatic causes (15). In this series of 865 MT events over a 4-year period, 30-day survival was not significantly different in patients who received a high plasma:PRBC ratio versus a low plasma:PRBC ratio. This finding, that a balanced plasma:PRBC ratio is not predictive of mortality in non-trauma patients, has been borne out in several other studies (59-61). Given the possible lack of benefit of a balanced resuscitation, is there a role for MTP activation for non-traumatic hemorrhage? Some studies would suggest that there is a benefit. One investigation from South Korea demonstrated improved coagulation profiles after the implementation of an MTP, without subsequent improvement in mortality (62). Another US-based study demonstrated similar outcomes pre- and post-MTP implementation, without any increase in hospital blood product usage (63). A systematic review and meta-analysis of 12 studies evaluating MTP in non-trauma patients found no change in number of blood products transfused and no difference in 24-hour mortality, with a trend towards lower 30-day mortality. The authors of this study note that this non-trauma population is quite heterogeneous, and thus multiple different patient-level factors may affect outcomes (64).

MT has been studied further in the management of obstetric hemorrhage, as this is a more homogenous patient population than combining all non-trauma causes of hemorrhage. While obstetric hemorrhage protocols have near universal support from major obstetric societies, the components of obstetric hemorrhage MTP's remains inconsistent. The American College of Obstetricians and Gynecologists (ACOG) recommends fixed product ratios (65). This practice is supported by retrospective studies that demonstrate, in combination with a comprehensive post-partum hemorrhage protocol, MTP is associated with improvement in transfusion needs and peri-partum hysterectomy (66-68). Additionally, obstetric hemorrhage protocols should focus on repletion of fibrinogen via early administration of CRYO or fibrinogen concentrate, as fibrinogen is the first coagulation factor to diminish in post-partum hemorrhage (69).

Pediatric patients also warrant careful consideration when assessing needs for MT. MT has been defined as ≥40 mL/kg of total blood products in the first 6 hours after injury or >1 total blood volume within 24 hours; other studies identified a threshold of 37 mL/kg at 4 hours as an inflection point predictive of increased need for hemorrhage control procedures and early mortality (70,71). In a recent meta-analysis, overall mortality for pediatric patients requiring MT was 15–51% (71). Given the changes in pediatric physiology, different scoring systems have been evaluated to predict the need for MT in this patient

population, as adult scoring systems have been proven to be less useful (72). In addition, FAST exam has limited utility in the pediatric population, making the ABC score less useful. Prehospital SI of >1.4 and SBP <100 have both been found to be highly specific for need for MT, with specificities of 86% and 92%, respectively, and 94% when both variables are present (73). Pediatric adjustment of the SI, SIPA, has been found to be modestly predictive of need for MT, and has been substituted for HR and SBP in the ABC score to form the ABC-S score (72,74). The ABC-D score, which adds base deficit and lactate to the ABC-S score, has the best AUROC of 0.805, but this has the disadvantage of requiring laboratory data to predict MT (75). While some studies have suggested a mortality benefit to a high-ratio plasma resuscitation in pediatric patients (76), others have failed to demonstrate this benefit in either military or civilian patient populations (77,78). Given these conflicting data, more research is needed to optimize the resuscitation of the severely injured pediatric patient. A recent survey demonstrated a strong willingness of pediatric trauma centers to participate in a randomized control trial (RCT) comparing LTOWB to component therapy in children with severe traumatic bleeding (79).

Adjuncts to MT

In addition to blood transfusion during MTP, several useful pharmacologic adjuncts to resuscitation have been identified. These include calcium repletion, tranexamic acid (TXA), factor VII concentrate, prothrombin complex concentrate (PCC), and arginine vasopressin (AVP). In addition to pharmacologic adjuncts, the use of viscoelastic testing can help improve blood product utilization and outcomes.

Calcium

MT is associated with severe hypocalcemia, which contributes to coagulopathy and mortality in severely injured trauma patients. Hypocalcemia is largely a result of the use of citrate as a blood anticoagulant, which chelates ionized calcium (iCa). Up to 97% of massively transfused trauma patients experience hypocalcemia (iCa <1.12 mmol/L), and severe hypocalcemia (iCa <0.9 mmol/L) was a significant risk factor for mortality (80). In fact, given its association with mortality, hypocalcemia has been proposed to be added to the lethal triad (hypothermia, coagulopathy, and acidosis) to form a "lethal diamond" (81). This hypocalcemia may also be an inherent response to severe injury, as it has been observed in severely injured trauma patients even prior to blood transfusion (82,83). Despite a robust body of literature demonstrating the connection between hypocalcemia and mortality, guidelines for empiric repletion of calcium are limited, and most guidance suggests repleting calcium levels once they are found to be low on laboratory monitoring. This may be partially due to the fact that over-repletion with resultant hypercalcemia (iCa >1.25 mmol/L) is also associated with increased mortality when compared to normal calcium levels. The Joint Trauma System Clinical Practice Guideline (CPG) for Damage Control Resuscitation suggests that 1 g of calcium chloride or 3 g of calcium gluconate be administered to patients in hemorrhagic shock during or immediately after the first unit of blood product transfusion and then with ongoing resuscitation after every 4 units of blood products, with monitoring of iCa and repletion if <1.2 mmol/L (84). Further evidence is needed to guide empiric calcium administration protocols and optimize calcium replacement.

TXA

TXA is a synthetic derivative of lysine that inhibits fibrinolysis by blocking the lysine binding sites on plasminogen, thus preventing the formation of plasmin and subsequent fibrin degradation. TXA has been demonstrated to decrease transfusion requirements and reduce blood loss in elective surgery without increasing post-operative complications (85). In addition, hyper-fibrinolysis has been identified as a phenotype of TIC that results in higher mortality (86). However, some amount of fibrinolysis during hemorrhage is physiologic, and inhibiting this presents a risk of increased vaso-occlusive events (87). The Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage trial (CRASH-2) was a landmark trial, published in 2010, which was the first large trial conducted studying the use of TXA in trauma patients (88). This randomized, placebo-controlled trial enrolled over 20,000 adult trauma patients in 274 hospitals in 40 countries, with, or at risk of, significant bleeding, and demonstrated a reduction in mortality from 16.0% to 14.5%, with a mortality from bleeding reduced from 5.7% to 4.9%. The strongest benefit was seen in the patients with the most severe shock (SBP ≤70 mmHg), and when administered ≤3 hours from injury, with a harm signal seen in administration after 3 hours (89). Limitations of this study were significant, however, in that this patient population

was fairly minimally injured, with only half of the patients even requiring a transfusion, and many of the participating centers lacked modern resuscitative practices. Nonetheless, TXA was added to the World Health Organization list of essential medications in 2011, given the potential for reduction in trauma-related deaths (90). Subsequently, multiple further studies have attempted to clarify the role of TXA in severely injured trauma patients, with mixed findings.

In the battlefield setting, TXA administration has been widely adopted based on the results of the Military Application of Tranexamic Acid in Trauma Emergency Resuscitation (MATTERs) studies, which demonstrated a mortality benefit, particularly in patients requiring MT (≥10 units/24 hours), but did also suggest an increase in thromboembolic events (91,92). Given controversy in patient selection, dosing, and potential for adverse events, the most recent guidelines endorsed by the American College of Surgeons Committee on Trauma recommend prehospital TXA administration in patients with evidence of non-compressible hemorrhage, along with HR >120 bpm and SBP <90 mmHg (93). In patients requiring MT, or in patients with documented evidence of hyperfibrinolysis on viscoelastic testing, the benefit of TXA is likely more robust, with evidence suggesting that earlier administration (within 3 hours from injury) is critical. Further trials are ongoing to better understand the role of TXA in hemorrhagic shock.

PCC

4-factor PCC (4F-PCC) is a pathogen-reduced, lyophilized concentrate that contains therapeutic amounts of vitamin K-dependent coagulation factors: factor II, VII, IX, and X. The use of PCC has been proposed as potential adjunct to help ameliorate the effects of TIC. PCC is widely used for the reversal of vitamin K-antagonist (VKA) anticoagulation and direct oral anticoagulant (DOAC) medications in the setting of major bleeding (94,95), but has also been used for patients with TIC without anticoagulant medication use. Potential benefits of PCC include rapidity of correction of coagulopathy, small volume of administration, and decreased transfusion-related complications; in light of these benefits, European guidelines suggest PCC as an adjunct to management of bleeding and coagulopathy following major trauma (96). Similar to TXA, the potential for thromboembolic events is a significant concern with overcorrection of coagulopathy. However, three retrospective studies evaluating the use of PCC in TIC have demonstrated a decrease in mortality, decreased transfusion requirements, and no increase in venous thromboembolism (97-99). Several multicenter prospective trials are currently underway that will add significantly to the understanding of the role of PCC in massive hemorrhage (100,101). PCC should be used in the setting of massive bleeding and known or suspected VKA or DOAC use. Of historical note, prior to the availability of PCC, recombinant factor VII had significant interest as an adjunct to MT; this is no longer used as a part of modern resuscitation practice.

AVP

Experts in resuscitation have long eschewed the use of vasopressors in the management of hemorrhagic shock, with the concern that they may rapidly increase arterial blood pressure, increase cardiac afterload, and cause arrhythmias and reduction in tissue perfusion with subsequent organ dysfunction and increased mortality (102). However, modern resuscitation research has revealed an increasing role for the very selective use of vasopressors to help ameliorate the late stages of hemorrhagic shock, where endogenous catecholamine and hormone depletion results in sympatho-inhibitory vasodilation and bradycardia (103). Recent research has focused on the use of AVP after finding that AVP levels are depleted in trauma patients with hemorrhagic shock (104). Two prospective randomized trials of AVP infusion have decreased transfusion requirements with equivalent outcomes in fluid/blood transfusion requirements (105,106). Further research is needed to define the optimal use of vasopressors, and more specifically AVP, in the patient requiring MT.

Viscoelastic testing

Monitoring of response to MT to tailor resuscitation is vital. In addition to examining hemodynamic response, monitoring laboratory response to transfusion is critical. Standard laboratory testing such as complete blood count (CBC), including Hb, HCT, and platelet count, along with measurement of electrolytes, is frequently performed. Laboratory measurement of coagulation function is somewhat more controversial. Use of prothrombin time (PT), INR, and activated partial thromboplastin time (aPTT) were developed to monitor response to VKAs and study factor deficiencies, and were not intended to guide therapy in bleeding patients with coagulopathy. Various comorbidities, in particular chronic liver disease,

may elevate PT and INR while not actually reflecting coagulopathy, depending on the balance of pro-and anticoagulant factors produced by an impaired liver (107). DOACs may also cause coagulopathy that is not reflected appropriately by PT or aPTT (108).

In light of these limitations of conventional laboratory testing, the use of viscoelastic testing has grown in popularity. Viscoelastic testing, including thromboelastography (TEG), rotational thromboelastometry (ROTEM), and newer sonometric methods (109), is performed by measuring timing and strength of blood clot development (110). These tests can be performed rapidly as a point-of-care test, with information on clot activation, kinetics, and strength available within 15 minutes (111). Given this favorable profile, multiple studies have demonstrated the utility of viscoelastic testing in predicting need for MT, predicting mortality, and helping improve resuscitation in a wide variety of patient populations, including cardiac surgery, liver transplant, trauma, and post-partum hemorrhage. Consistent with multiple retrospective studies, a recent randomized trial in trauma patients comparing TEG to standard coagulation-guided resuscitation showed a survival benefit at 28 days as well as fewer platelet and plasma transfusions (112-114). In post-partum hemorrhage, given the critical nature of fibrinogen repletion, viscoelastic testing has been advocated to determine early fibrinogen deficiency as well as hyper-fibrinolysis, although reference values are still not well-defined (115). In elective cardiac surgery, ROTEM-guided coagulation management has been demonstrated to decrease transfusion requirement, decrease cost, and decrease post-operative bleeding (116).

Complications of MT

Adverse effects of blood transfusions can result in a multitude of complications. One in 455 blood components transfused is associated with an adverse event, but the risk of serious adverse reactions (1 in 6,224) and transfusion-transmitted infections (1 in 255,400) is extremely low in the United States (117). The most common non-infectious reactions include febrile non-hemolytic transfusion reactions, allergic transfusion reactions, transfusion-associated circulatory overload (TACO), transfusion-related acute lung injury (TRALI), and acute or delayed hemolytic reactions (118). The effects of blood preservation and storage also cause changes in the quality of the blood over time, including decreased pH, increased potassium, decreased 2,3-diphosphoglycerate (2,3-DPG), and decreases in erythrocyte and platelet function, all of which may affect resuscitation and oxygen delivery (119).

Patients undergoing MT are exposed to large quantities of blood from multiple donors, increasing potential complication rates. Multiple studies suggest a relationship between blood product transfusion and multiple organ failure as well as other serious adverse outcomes, although they are unable to distinguish between risk of transfusion and the need of transfusion as a marker of severity of injury (i.e., confounding by indication) (120,121). Case in point, large volume transfusion has been associated with higher rates of infectious complication and lung injury due to volume overload, while the implementation of a MTP results in lower rates of pneumonia, pulmonary failure, abdominal compartment syndrome, sepsis, and multiple organ failure (122,123). Pulmonary involvement due to transfusions in the setting of MT usually presents as either TRALI or TACO. TRALI has been defined as the presence of hypoxemia [partial pressure of oxygen (PaO_2)/fraction of inspired oxygen (FiO_2) ≤300 or oxygen saturation (SpO_2) <90% on room air], with bilateral infiltrates on chest radiograph and no evidence of circulatory overload. This definition has recently been updated (124). TRALI is relatively rare in modern resuscitation, with an incidence as low as approximately 1 case per 100,000 units transfused being reported recently (125). Exposure to human leukocyte antigen (HLA) antibodies or other biologic response modifiers in blood products is the main factor implicated in the development of TRALI, with subsequent inflammation triggering increased capillary permeability. The use of male-predominant donors to reduce HLA antibodies present in plasma has significantly reduced rates of TRALI (126). TACO is more common and is essentially cardiogenic pulmonary edema that has an incidence of up to 11% in critically ill patients (127). The definition of TACO was recently revised and now allows for suspected reactions to be reported up to 12 hours after transfusion (128). TACO is partly related to the volume of blood transfused, but in one cohort studied, 50% of TACO cases occurred after a single unit of blood transfused, prompting the theory that a "two-hit" model, with pre-existing cardiopulmonary comorbidities combined with blood product factors such as pro-inflammatory mediators, storage lesion byproducts, and osmotic pressure effects are the driving factors in the development of TACO (129).

As part of an MTP, patients can receive uncrossmatched transfusions from universal donor blood products prior to the completion of required blood bank testing and issuing

of crossmatched blood products. RBC alloimmunization is an inherent risk in this process. Rh(D)-negative patients exposed to Rh(D)-positive blood products are at risk of developing anti-D antibodies, and these alloimmunized patients can develop hemolytic transfusion reactions or, in those women who later become pregnant, hemolytic disease of the fetus and newborn. In healthy individuals, this rate is approximately 80%, but in trauma patients there appears to be a range of lower alloimmunization risks, with rates of only 8% up to 50% in recent series (130-133).

Future directions

There is much that is still unknown about the optimal management of the patient requiring MT, whether it be for traumatic hemorrhage, obstetric hemorrhage, or any other indication. Much of the literature on MT is specific to trauma patients; the generalizability of this research to the non-trauma patient population is not known and is an area for future investigations. The optimal use of component therapy versus LTOWB is also an area of significant current investigation, with multiple randomized controlled trials underway. Understanding the mechanisms underlying TIC, and how this state may apply to other patients with non-traumatic hemorrhagic shock, will help elucidate best management strategies for these patients. Future investigations will also help optimize the use of pharmacologic adjuncts to resuscitation including use of PCC, TXA, and other medications.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editor (Paul D. Mintz) for the series "Transfusion Therapy: Principles and Practices" published in *Annals of Blood*. The article has undergone external peer review.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://aob.amegroups.com/article/view/10.21037/aob-22-3/coif). The series "Transfusion Therapy: Principles and Practices" was commissioned by the editorial office without any funding or sponsorship. JSR is a consultant, advisor and speaker for Sanofi Genzyme and Terumo BCT. These involve development of treatment algorithms for thrombotic thrombocytopenic purpura and applications for therapeutic apheresis, respectively. JSR is also on the Board of Directors of American Society for Apheresis. There is no overlap with the content contained in the current manuscript. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Repine TB, Perkins JG, Kauvar DS, et al. The use of fresh whole blood in massive transfusion. J Trauma 2006;60:S59-69.
2. Hess JR, Thomas MJ. Blood use in war and disaster: lessons from the past century. Transfusion 2003;43:1622-33.
3. Yazer MH, Spinella PC. The use of low-titer group O whole blood for the resuscitation of civilian trauma patients in 2018. Transfusion 2018;58:2744-6.
4. Dailey RH. "Code Red" protocol for resuscitation of the exsanguinated patient. J Emerg Med 1985;2:373-8.
5. Schuster KM, Davis KA, Lui FY, et al. The status of massive transfusion protocols in United States trauma centers: massive transfusion or massive confusion? Transfusion 2010;50:1545-51.
6. Etchill E, Sperry J, Zuckerbraun B, et al. The confusion continues: results from an American Association for the Surgery of Trauma survey on massive transfusion practices among United States trauma centers. Transfusion 2016;56:2478-86.
7. Thomasson RR, Yazer MH, Gorham JD, et al. International assessment of massive transfusion protocol contents and indications for activation. Transfusion

2019;59:1637-43.
8. Savage SA, Zarzaur BL, Croce MA, et al. Redefining massive transfusion when every second counts. J Trauma Acute Care Surg 2013;74:396-400; discussion 400-2.
9. Rahbar E, Fox EE, del Junco DJ, et al. Early resuscitation intensity as a surrogate for bleeding severity and early mortality in the PROMMTT study. J Trauma Acute Care Surg 2013;75:S16-23.
10. Meyer DE, Cotton BA, Fox EE, et al. A comparison of resuscitation intensity and critical administration threshold in predicting early mortality among bleeding patients: A multicenter validation in 680 major transfusion patients. J Trauma Acute Care Surg 2018;85:691-6.
11. Hu P, Uhlich R, Black J, et al. A new definition for massive transfusion in the modern era of whole blood resuscitation. Transfusion 2021;61 Suppl 1:S252-63.
12. JPAC. 7.3: Transfusion management of major haemorrhage. 2018. Available online: https://www.transfusionguidelines.org/transfusion-handbook/7-effective-transfusion-in-surgery-and-critical-care/7-3-transfusion-management-of-major-haemorrhage
13. Como JJ, Dutton RP, Scalea TM, et al. Blood transfusion rates in the care of acute trauma. Transfusion 2004;44:809-13.
14. Halmin M, Chiesa F, Vasan SK, et al. Epidemiology of Massive Transfusion: A Binational Study From Sweden and Denmark. Crit Care Med 2016;44:468-77.
15. Mesar T, Larentzakis A, Dzik W, et al. Association Between Ratio of Fresh Frozen Plasma to Red Blood Cells During Massive Transfusion and Survival Among Patients Without Traumatic Injury. JAMA Surg 2017;152:574-80.
16. Brohi K, Singh J, Heron M, et al. Acute traumatic coagulopathy. J Trauma 2003;54:1127-30.
17. Moore EE, Moore HB, Kornblith LZ, et al. Trauma-induced coagulopathy. Nat Rev Dis Primers 2021;7:30.
18. Moore EE. Thomas G. Orr Memorial Lecture. Staged laparotomy for the hypothermia, acidosis, and coagulopathy syndrome. Am J Surg 1996;172:405-10.
19. Kornblith LZ, Moore HB, Cohen MJ. Trauma-induced coagulopathy: The past, present, and future. J Thromb Haemost 2019;17:852-62.
20. Hoffman M, Monroe DM 3rd. A cell-based model of hemostasis. Thromb Haemost 2001;85:958-65.
21. Wu F, Chipman A, Pati S, et al. Resuscitative Strategies to Modulate the Endotheliopathy of Trauma: From Cell to Patient. Shock 2020;53:575-84.
22. Cantle PM, Cotton BA. Prediction of Massive Transfusion in Trauma. Crit Care Clin 2017;33:71-84.
23. Nunez TC, Dutton WD, May AK, et al. Emergency department blood transfusion predicts early massive transfusion and early blood component requirement. Transfusion 2010;50:1914-20.
24. Pommerening MJ, Goodman MD, Holcomb JB, et al. Clinical gestalt and the prediction of massive transfusion after trauma. Injury 2015;46:807-13.
25. Schroll R, Swift D, Tatum D, et al. Accuracy of shock index versus ABC score to predict need for massive transfusion in trauma patients. Injury 2018;49:15-9.
26. Yücel N, Lefering R, Maegele M, et al. Trauma Associated Severe Hemorrhage (TASH)-Score: probability of mass transfusion as surrogate for life threatening hemorrhage after multiple trauma. J Trauma 2006;60:1228-36; discussion 1236-7.
27. McLaughlin DF, Niles SE, Salinas J, et al. A predictive model for massive transfusion in combat casualty patients. J Trauma 2008;64:S57-63; discussion S63.
28. Koch E, Lovett S, Nghiem T, et al. Shock index in the emergency department: utility and limitations. Open Access Emerg Med 2019;11:179-99.
29. Nunez TC, Voskresensky IV, Dossett LA, et al. Early prediction of massive transfusion in trauma: simple as ABC (assessment of blood consumption)? J Trauma 2009;66:346-52.
30. Cotton BA, Dossett LA, Haut ER, et al. Multicenter validation of a simplified score to predict massive transfusion in trauma. J Trauma 2010;69 Suppl 1:S33-9.
31. Weaver AE, Hunter-Dunn C, Lyon RM, et al. The effectiveness of a 'Code Red' transfusion request policy initiated by pre-hospital physicians. Injury 2016;47:3-6.
32. Dunbar NM, Yazer MH. Confusion surrounding trauma resuscitation and opportunities for clarification. Transfusion 2020;60 Suppl 3:S142-9.
33. O'Keeffe T, Refaai M, Tchorz K, et al. A massive transfusion protocol to decrease blood component use and costs. Arch Surg 2008;143:686-90; discussion 690-1.
34. Holcomb JB, Tilley BC, Baraniuk S, et al. Transfusion of plasma, platelets, and red blood cells in a 1:1:1 vs a 1:1:2 ratio and mortality in patients with severe trauma: the PROPPR randomized clinical trial. JAMA 2015;313:471-82.
35. Meyer DE, Vincent LE, Fox EE, et al. Every minute counts: Time to delivery of initial massive transfusion cooler and its impact on mortality. J Trauma Acute Care Surg 2017;83:19-24.
36. Matthay ZA, Hellmann ZJ, Callcut RA, et al. Outcomes after ultramassive transfusion in the modern era: An Eastern Association for the Surgery of Trauma multicenter study. J Trauma Acute Care Surg 2021;91:24-33.

37. Armand R, Hess JR. Treating coagulopathy in trauma patients. Transfus Med Rev 2003;17:223-31.
38. Spinella PC, Perkins JG, Grathwohl KW, et al. Warm fresh whole blood is independently associated with improved survival for patients with combat-related traumatic injuries. J Trauma 2009;66:S69-76.
39. Katsura M, Matsushima K, Kitamura R, et al. The use of warm fresh whole blood transfusion in the austere setting: A civilian trauma experience. J Trauma Acute Care Surg 2020;89:e28-33.
40. Seheult JN, Bahr M, Anto V, et al. Safety profile of uncrossmatched, cold-stored, low-titer, group O+ whole blood in civilian trauma patients. Transfusion 2018;58:2280-8.
41. Yazer MH, Spinella PC, Anto V, et al. Survey of group A plasma and low-titer group O whole blood use in trauma resuscitation at adult civilian level 1 trauma centers in the US. Transfusion 2021;61:1757-63.
42. AABB. Standards for blood banks and transfusion services. 32nd ed. Bethesda: AABB, 2020.
43. Shea SM, Staudt AM, Thomas KA, et al. The use of low-titer group O whole blood is independently associated with improved survival compared to component therapy in adults with severe traumatic hemorrhage. Transfusion 2020;60 Suppl 3:S2-9.
44. Hazelton JP, Cannon JW, Zatorski C, et al. Cold-stored whole blood: A better method of trauma resuscitation? J Trauma Acute Care Surg 2019;87:1035-41.
45. Duchesne J, Smith A, Lawicki S, et al. Single Institution Trial Comparing Whole Blood vs Balanced Component Therapy: 50 Years Later. J Am Coll Surg 2021;232:433-42.
46. Martinaud C, Tiberghien P, Bégué S, et al. Rational and design of the T-STORHM Study: A prospective randomized trial comparing fresh whole blood to blood components for acutely bleeding trauma patients. Transfus Clin Biol 2019;26:198-201.
47. Gálvez J, Hsu G, Dubow S, et al. How do I…Incorporate a two-sample blood type verification in a pediatric hospital? Transfusion 2020;60:2787-92.
48. Dunbar NM, Yazer MH; Biomedical Excellence for Safer Transfusion (BEST) Collaborative and the STAT Study Investigators. Safety of the use of group A plasma in trauma: the STAT study. Transfusion 2017;57:1879-84.
49. Seheult JN, Dunbar NM, Hess JR, et al. Transfusion of blood components containing ABO-incompatible plasma does not lead to higher mortality in civilian trauma patients. Transfusion 2020;60:2517-28.
50. Yazer MH, Spinella PC, Doyle L, et al. Transfusion of Uncrossmatched Group O Erythrocyte-containing Products Does Not Interfere with Most ABO Typings. Anesthesiology 2020;132:525-34.
51. Murrell Z, Haukoos JS, Putnam B, et al. The effect of older blood on mortality, need for ICU care, and the length of ICU stay after major trauma. Am Surg 2005;71:781-5.
52. Cohn SM, DeRosa M, Kumar A, et al. Impact of the age of transfused red blood cells in the trauma population: a feasibility study. Injury 2014;45:605-11.
53. McDaniel LM, Triulzi DJ, Cramer J, et al. Massive transfusion protocol activation does not result in preferential use of older red blood cells. J Blood Transfus 2014;2014:328967.
54. McDaniel LM, Neal MD, Sperry JL, et al. Use of a massive transfusion protocol in nontrauma patients: activate away. J Am Coll Surg 2013;216:1103-9.
55. Cotton BA, Dossett LA, Au BK, et al. Room for (performance) improvement: provider-related factors associated with poor outcomes in massive transfusion. J Trauma 2009;67:1004-12.
56. Bawazeer M, Ahmed N, Izadi H, et al. Compliance with a massive transfusion protocol (MTP) impacts patient outcome. Injury 2015;46:21-8.
57. Nunez TC, Young PP, Holcomb JB, et al. Creation, implementation, and maturation of a massive transfusion protocol for the exsanguinating trauma patient. J Trauma 2010;68:1498-505.
58. Yazer MH, Dunbar NM, Cohn C, et al. Blood product transfusion and wastage rates in obstetric hemorrhage. Transfusion 2018;58:1408-13.
59. Warner MA, Frank RD, Weister TJ, et al. Ratios of Plasma and Platelets to Red Blood Cells in Surgical Patients With Acute Intraoperative Hemorrhage. Anesth Analg 2020;131:483-93.
60. Matzek LJ, Kurian EB, Frank RD, et al. Plasma, platelet and red blood cell transfusion ratios for life-threatening non-traumatic haemorrhage in medical and post-surgical patients: An observational study. Vox Sang 2022;117:361-70.
61. Etchill EW, Myers SP, McDaniel LM, et al. Should All Massively Transfused Patients Be Treated Equally? An Analysis of Massive Transfusion Ratios in the Nontrauma Setting. Crit Care Med 2017;45:1311-6.
62. Yoon KW, Cho D, Lee DS, et al. Clinical impact of massive transfusion protocol implementation in non-traumatic patients. Transfus Apher Sci 2020;59:102631.
63. Baumann Kreuziger LM, Morton CT, Subramanian

AT, et al. Not only in trauma patients: hospital-wide implementation of a massive transfusion protocol. Transfus Med 2014;24:162-8.
64. Sommer N, Schnüriger B, Candinas D, et al. Massive transfusion protocols in nontrauma patients: A systematic review and meta-analysis. J Trauma Acute Care Surg 2019;86:493-504.
65. Committee on Practice Bulletins-Obstetrics. Practice Bulletin No. 183: Postpartum Hemorrhage. Obstet Gynecol 2017;130:e168-86.
66. Shields LE, Wiesner S, Fulton J, et al. Comprehensive maternal hemorrhage protocols reduce the use of blood products and improve patient safety. Am J Obstet Gynecol 2015;212:272-80.
67. O'Brien KL, Shainker SA, Lockhart EL. Transfusion Management of Obstetric Hemorrhage. Transfus Med Rev 2018;32:249-55.
68. Shaylor R, Weiniger CF, Austin N, et al. National and International Guidelines for Patient Blood Management in Obstetrics: A Qualitative Review. Anesth Analg 2017;124:216-32.
69. Charbit B, Mandelbrot L, Samain E, et al. The decrease of fibrinogen is an early predictor of the severity of postpartum hemorrhage. J Thromb Haemost 2007;5:266-73.
70. Rosenfeld E, Lau P, Zhang W, et al. Defining massive transfusion in civilian pediatric trauma. J Pediatr Surg 2019;54:975-9.
71. Kamyszek RW, Leraas HJ, Reed C, et al. Massive transfusion in the pediatric population: A systematic review and summary of best-evidence practice strategies. J Trauma Acute Care Surg 2019;86:744-54.
72. Acker SN, Hall B, Hill L, et al. Adult-Based Massive Transfusion Protocol Activation Criteria Do Not Work in Children. Eur J Pediatr Surg 2017;27:32-5.
73. Zhu CS, Braverman M, Goddard S, et al. Prehospital shock index and systolic blood pressure are highly specific for pediatric massive transfusion. J Trauma Acute Care Surg 2021;91:579-83.
74. Acker SN, Bredbeck B, Partrick DA, et al. Shock index, pediatric age-adjusted (SIPA) is more accurate than age-adjusted hypotension for trauma team activation. Surgery 2017;161:803-7.
75. Phillips R, Acker SN, Shahi N, et al. The ABC-D score improves the sensitivity in predicting need for massive transfusion in pediatric trauma patients. J Pediatr Surg 2020;55:331-4.
76. Noland DK, Apelt N, Greenwell C, et al. Massive transfusion in pediatric trauma: An ATOMAC perspective. J Pediatr Surg 2019;54:345-9.
77. Sehdev M, Grigorian A, Kuza C, et al. Comparing unbalanced and balanced ratios of blood products in massive transfusion to pediatric trauma patients: effects on mortality and outcomes. Eur J Trauma Emerg Surg 2022;48:179-86.
78. Cannon JW, Johnson MA, Caskey RC, et al. High ratio plasma resuscitation does not improve survival in pediatric trauma patients. J Trauma Acute Care Surg 2017;83:211-7.
79. Kolodziej JH, Leonard JC, Josephson CD, et al. Survey to inform trial of low-titer group O whole-blood compared to conventional blood components for children with severe traumatic bleeding. Transfusion 2021;61 Suppl 1:S43-8.
80. Giancarelli A, Birrer KL, Alban RF, et al. Hypocalcemia in trauma patients receiving massive transfusion. J Surg Res 2016;202:182-7.
81. Ditzel RM Jr, Anderson JL, Eisenhart WJ, et al. A review of transfusion- and trauma-induced hypocalcemia: Is it time to change the lethal triad to the lethal diamond? J Trauma Acute Care Surg 2020;88:434-9.
82. Webster S, Todd S, Redhead J, et al. Ionised calcium levels in major trauma patients who received blood in the Emergency Department. Emerg Med J 2016;33:569-72.
83. Magnotti LJ, Bradburn EH, Webb DL, et al. Admission ionized calcium levels predict the need for multiple transfusions: a prospective study of 591 critically ill trauma patients. J Trauma 2011;70:391-5; discussion 395-7.
84. Joint Trauma System Clinical Practice Guideline. Damage Control Resuscitation (CPG ID:18). 2019. Available online: https://jts.amedd.army.mil/assets/docs/cpgs/Damage_Control_Resuscitation_12_Jul_2019_ID18.pdf
85. Henry DA, Carless PA, Moxey AJ, et al. Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion. Cochrane Database Syst Rev 2011;(1):CD001886.
86. Moore HB, Moore EE, Liras IN, et al. Acute Fibrinolysis Shutdown after Injury Occurs Frequently and Increases Mortality: A Multicenter Evaluation of 2,540 Severely Injured Patients. J Am Coll Surg 2016;222:347-55.
87. Wirtz MR, Schalkers DV, Goslings JC, et al. The impact of blood product ratio and procoagulant therapy on the development of thromboembolic events in severely injured hemorrhaging trauma patients. Transfusion 2020;60:1873-82.
88. CRASH-2 trial collaborators; Shakur H, Roberts I, et al. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised,

placebo-controlled trial. Lancet 2010;376:23-32.
89. CRASH-2 collaborators; Roberts I, Shakur H, et al. The importance of early treatment with tranexamic acid in bleeding trauma patients: an exploratory analysis of the CRASH-2 randomised controlled trial. Lancet 2011;377:1096-101, 1101.e1-2.
90. Summary of the report of the 18th meeting of the WHO Expert Committee on the Selection and Use of Essential Medicines, 18th Meeting, Accra, Ghana March 21Y25, 2011. 2011 [cited 2021 October 19]. Available online: https://www.who.int/publications/i/item/9789241209656
91. Morrison JJ, Dubose JJ, Rasmussen TE, et al. Military Application of Tranexamic Acid in Trauma Emergency Resuscitation (MATTERs) Study. Arch Surg 2012;147:113-9.
92. Morrison JJ, Ross JD, Dubose JJ, et al. Association of cryoprecipitate and tranexamic acid with improved survival following wartime injury: findings from the MATTERs II Study. JAMA Surg 2013;148:218-25.
93. Fischer PE, Bulger EM, Perina DG, et al. Guidance Document for the Prehospital Use of Tranexamic Acid in Injured Patients. Prehosp Emerg Care 2016;20:557-9.
94. Sarode R, Milling TJ Jr, Refaai MA, et al. Efficacy and safety of a 4-factor prothrombin complex concentrate in patients on vitamin K antagonists presenting with major bleeding: a randomized, plasma-controlled, phase IIIb study. Circulation 2013;128:1234-43.
95. Milioglou I, Farmakis I, Neudeker M, et al. Prothrombin complex concentrate in major bleeding associated with DOACs; an updated systematic review and meta-analysis. J Thromb Thrombolysis 2021;52:1137-50.
96. Spahn DR, Bouillon B, Cerny V, et al. Management of bleeding and coagulopathy following major trauma: an updated European guideline. Crit Care 2013;17:R76.
97. Zeeshan M, Hamidi M, Feinstein AJ, et al. Four-factor prothrombin complex concentrate is associated with improved survival in trauma-related hemorrhage: A nationwide propensity-matched analysis. J Trauma Acute Care Surg 2019;87:274-81.
98. Jehan F, Aziz H, O'Keeffe T, et al. The role of four-factor prothrombin complex concentrate in coagulopathy of trauma: A propensity matched analysis. J Trauma Acute Care Surg 2018;85:18-24.
99. Joseph B, Aziz H, Pandit V, et al. Prothrombin complex concentrate versus fresh-frozen plasma for reversal of coagulopathy of trauma: is there a difference? World J Surg 2014;38:1875-81.
100. da Luz LT, Callum J, Beckett A, et al. Protocol for a multicentre, randomised, parallel-control, superiority trial comparing administration of clotting factor concentrates with a standard massive haemorrhage protocol in severely bleeding trauma patients: the FiiRST 2 trial (a 2020 EAST multicentre trial). BMJ Open 2021;11:e051003.
101. Bouzat P, Bosson JL, David JS, et al. Four-factor prothrombin complex concentrate to reduce allogenic blood product transfusion in patients with major trauma, the PROCOAG trial: study protocol for a randomized multicenter double-blind superiority study. Trials 2021;22:634.
102. Uchida K, Nishimura T, Hagawa N, et al. The impact of early administration of vasopressor agents for the resuscitation of severe hemorrhagic shock following blunt trauma. BMC Emerg Med 2020;20:26.
103. Richards JE, Harris T, Dünser MW, et al. Vasopressors in Trauma: A Never Event? Anesth Analg 2021;133:68-79.
104. Sims CA, Guan Y, Bergey M, et al. Arginine vasopressin, copeptin, and the development of relative AVP deficiency in hemorrhagic shock. Am J Surg 2017;214:589-95.
105. Sims CA, Holena D, Kim P, et al. Effect of Low-Dose Supplementation of Arginine Vasopressin on Need for Blood Product Transfusions in Patients With Trauma and Hemorrhagic Shock: A Randomized Clinical Trial. JAMA Surg 2019;154:994-1003.
106. Cohn SM, McCarthy J, Stewart RM, et al. Impact of low-dose vasopressin on trauma outcome: prospective randomized study. World J Surg 2011;35:430-9.
107. Caldwell SH, Hoffman M, Lisman T, et al. Coagulation disorders and hemostasis in liver disease: pathophysiology and critical assessment of current management. Hepatology 2006;44:1039-46.
108. Adcock DM, Gosselin RC. The danger of relying on the APTT and PT in patients on DOAC therapy, a potential patient safety issue. Int J Lab Hematol 2017;39 Suppl 1:37-40.
109. Carll T, Wool GD. Basic principles of viscoelastic testing. Transfusion 2020;60 Suppl 6:S1-9.
110. Faraoni D, DiNardo JA. Viscoelastic hemostatic assays: Update on technology and clinical applications. Am J Hematol 2021;96:1331-7.
111. Pezold M, Moore EE, Wohlauer M, et al. Viscoelastic clot strength predicts coagulation-related mortality within 15 minutes. Surgery 2012;151:48-54.
112. Veigas PV, Callum J, Rizoli S, et al. A systematic review on the rotational thrombelastometry (ROTEM®) values for the diagnosis of coagulopathy, prediction and guidance

of blood transfusion and prediction of mortality in trauma patients. Scand J Trauma Resusc Emerg Med 2016;24:114.
113. Gonzalez E, Moore EE, Moore HB, et al. Goal-directed Hemostatic Resuscitation of Trauma-induced Coagulopathy: A Pragmatic Randomized Clinical Trial Comparing a Viscoelastic Assay to Conventional Coagulation Assays. Ann Surg 2016;263:1051-9.
114. Brill JB, Brenner M, Duchesne J, et al. The Role of TEG and ROTEM in Damage Control Resuscitation. Shock 2021;56:52-61.
115. Liew-Spilger AE, Sorg NR, Brenner TJ, et al. Viscoelastic Hemostatic Assays for Postpartum Hemorrhage. J Clin Med 2021;10:3946.
116. Haas T, Görlinger K, Grassetto A, et al. Thromboelastometry for guiding bleeding management of the critically ill patient: a systematic review of the literature. Minerva Anestesiol 2014;80:1320-35.
117. Kracalik I, Mowla S, Basavaraju SV, et al. Transfusion-related adverse reactions: Data from the National Healthcare Safety Network Hemovigilance Module - United States, 2013-2018. Transfusion 2021;61:1424-34.
118. Goel R, Tobian AAR, Shaz BH. Noninfectious transfusion-associated adverse events and their mitigation strategies. Blood 2019;133:1831-9.
119. Längst E, Tissot JD, Prudent M. Storage of red blood cell concentrates: Clinical impact. Transfus Clin Biol 2021;28:397-402.
120. MacLeod J, Lynn M, McKenney MG, et al. Predictors of mortality in trauma patients. Am Surg 2004;70:805-10.
121. Middelburg RA, van de Watering LM, van der Bom JG. Blood transfusions: good or bad? Confounding by indication, an underestimated problem in clinical transfusion research. Transfusion 2010;50:1181-3.
122. Cotton BA, Au BK, Nunez TC, et al. Predefined massive transfusion protocols are associated with a reduction in organ failure and postinjury complications. J Trauma 2009;66:41-8; discussion 48-9.
123. Vogt KN, Van Koughnett JA, Dubois L, et al. The use of trauma transfusion pathways for blood component transfusion in the civilian population: a systematic review and meta-analysis. Transfus Med 2012;22:156-66.
124. Vlaar APJ, Toy P, Fung M, et al. An update of the transfusion-related acute lung injury (TRALI) definition. Transfus Clin Biol 2019;26:354-6.
125. Meyer DE, Reynolds JW, Hobbs R, et al. The Incidence of Transfusion-Related Acute Lung Injury at a Large, Urban Tertiary Medical Center: A Decade's Experience. Anesth Analg 2018;127:444-9.
126. Toy P, Gajic O, Bacchetti P, et al. Transfusion-related acute lung injury: incidence and risk factors. Blood 2012;119:1757-67.
127. Lieberman L, Maskens C, Cserti-Gazdewich C, et al. A retrospective review of patient factors, transfusion practices, and outcomes in patients with transfusion-associated circulatory overload. Transfus Med Rev 2013;27:206-12.
128. Wiersum-Osselton JC, Whitaker B, Grey S, et al. Revised international surveillance case definition of transfusion-associated circulatory overload: a classification agreement validation study. Lancet Haematol 2019;6:e350-8.
129. Bulle EB, Klanderman RB, Pendergrast J, et al. The recipe for TACO: A narrative review on the pathophysiology and potential mitigation strategies of transfusion-associated circulatory overload. Blood Rev 2022;52:100891.
130. Raval JS, Madden KM, Neal MD, et al. Anti-D alloimmunization in Rh(D) negative adults with severe traumatic injury. Transfusion 2021;61 Suppl 1:S144-9.
131. Flommersfeld S, Mand C, Kühne CA, et al. Unmatched Type O RhD+ Red Blood Cells in Multiple Injured Patients. Transfus Med Hemother 2018;45:158-61.
132. Yazer MH, Triulzi DJ, Sperry JL, et al. Rate of RhD-alloimmunization after the transfusion of multiple RhD-positive primary red blood cell-containing products. Transfusion 2021;61 Suppl 1:S150-8.
133. Yazer M, Triulzi D, Sperry J, et al. Rate of RhD-alloimmunization after the transfusion of RhD-positive red blood cell containing products among injured patients of childbearing age: single center experience and narrative literature review. Hematology 2021;26:321-7.

doi: 10.21037/aob-22-3
Cite this article as: Moore SA, Raval JS. Massive transfusion: a review. Ann Blood 2022;7:18.

