Optimal Fluid Therapy for Traumatic Hemorrhagic Shock

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KEYWORDS

• Massive transfusion protocol • Hemorrhagic shock • Damage control resuscitation

KEY POINTS

- Hemorrhage is the leading cause of preventable trauma deaths and occurs rapidly (median 2–3 hours after presentation).
- Early activation of a predefined massive transfusion protocol improves outcomes for the patient with exsanguinating hemorrhage, although accurate identification remains a challenge.
- Large infusions of crystalloid are dangerous for patients with traumatic hemorrhagic shock, and even relatively small volumes of crystalloid may be harmful.
- Plasma should be used as the primary means of volume expansion for resuscitation of trauma patients with hemorrhagic shock.
- Although the exact mechanisms underlying the benefits of plasma are unclear, it is likely more than simple replacement of volume and clotting factors.

INTRODUCTION

Hemorrhage is a top cause of death after injury and is the leading cause of potentially preventable trauma deaths.[1–3] In contrast to other causes of trauma death, such as traumatic brain injury (TBI), multiple organ dysfunction syndrome (MODS), and sepsis, exsanguination occurs rapidly with a median time to death of 2 to 3 hours after presentation.[4,5] Advances in the treatment of hemorrhagic shock have historically been made during times of armed conflict: major milestones include the first blood banks during World War I, the development of dried plasma during World War II, recognition of a close association between shock and coagulopathy during the Vietnam War,[6] and the advent of damage control resuscitation (DCR) during the recent wars in

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Afghanistan and Iraq. DCR was a paradigm shift in the management of traumatic hemorrhagic shock and is a major focus of this article.

As the management of trauma evolves over time, experts are discovering more and more that resuscitation of the severely injured patient (the normalization of deranged physiology and correction of the shock state) has as much impact on patient outcome as surgical treatment of the injured tissues. Development of an optimal resuscitation strategy with attention to the type, quantity, and timing of fluid therapy is of paramount importance to any clinician caring for trauma patients presenting with hemorrhagic shock.

PATIENT EVALUATION OVERVIEW

A small minority (1%–3%) of patients presenting to a major urban trauma center will require substantial blood product transfusion following injury, typically referred to as massive transfusion (MT). Traditionally, MT had been arbitrarily defined as transfusion of at least 10 units of packed red blood cells (PRBCs) within 24 hours. Early identification of the trauma patient who will require MT is difficult but nonetheless essential because early activation of a predefined MT protocol (MTP) is associated with decreased blood product waste,[7] as well as reduced incidence of organ failure and other complications.[8]

Several scoring systems have been proposed to predict need for MT but early iterations, such as the Trauma Associated Severe Hemorrhage (TASH) score[9] and the McLaughlin score,[10] relied on laboratory values that are not available until some time after presentation. In 2010, Cotton and colleagues[11] published a multicenter validation study of the Assessment of Blood Consumption (ABC) score, which gives 1 point for each of the following: penetrating mechanism, systolic blood pressure (SBP) less than 90 mm Hg, heart rate greater than 120 beats per minute, and positive Focused Abdominal Sonography in Trauma (FAST) examination (**Boxes 1** and **2**).

A score of 2 or more is predictive of MT with a sensitivity of 75% to 90%, specificity of 67% to 88%, and overall accuracy of 84% to 87% for all trauma patients. Importantly, the ABC score requires no laboratory data, can be determined within minutes of patient arrival, and can be easily recalculated over time. The American College of Surgeons (ACS) Trauma Quality Improvement Program (TQIP) Massive Transfusion in Trauma Guidelines now recommends use of the ABC score of 2 or more for MTP activation.

Pommerening and colleagues[12] examined the reliability of physician gestalt in predicting need for MT by performing a secondary analysis on subjects from the Prospective, Observational, Multicenter, Major Trauma Transfusion (PROMMTT) study. Of note, entry into this study required transfusion of at least 1 PRBC unit within the first 6 hours, and subjects who died within 30 minutes of presentation were excluded.

Box 1
Assessment of blood consumption score. Score of 2 or more points predicted need for massive transfusion within 24 hours with sensitivity 75% to 90%, specificity 67% to 86%, and overall accuracy 84% to 86%

- Penetrating mechanism (no = 0; yes = 1)
- Emergency department SBP less than 90 mm Hg (no = 0; yes = 1)
- Emergency department heart rate greater than 120 bpm (no = 0; yes = 1)
- Positive Focused Abdominal Sonography in Trauma (FAST) examination (no = 0; yes = 1)

Box 2
Initiate massive transfusion protocol (MTP) if one or more of the following criteria are met

- ABC score of 2 or more
- Persistent hemodynamic instability
- Active bleeding requiring operation or angioembolization
- Blood transfusion in the trauma bay

Adapted from ACS TQIP. Massive Transfusion in Trauma Guidelines. American College of Surgeons. Available at: https://www.facs.org/%7E/media/files/quality%20programs/trauma/tqip/massive%20transfusion%20in%20trauma%20guildelines.ashx. Accessed April 13, 2016.

Therefore, included subjects were at overall intermediate risk for requiring MT, whereas subjects at the 2 extremes were excluded. In this subject group, investigators found that physician gestalt and several scoring systems, including ABC, performed relatively poorly, achieving modest sensitivities and specificities of 65% to 70%. Independent predictors of a false-negative physician gestalt were bleeding in the pelvis and relatively normal blood gas parameters.

Viscoelastic assays of coagulation (thromboelastography [TEG] and rotational thromboelastometry [ROTEM]) can be used to diagnose and monitor trauma-induced coagulopathy. Because clinically meaningful results can be available within minutes of trauma patient arrival, TEG and ROTEM have been proposed as predictors of need for MT. Prospective observational studies by Cotton and colleagues[13] and Davenport and colleagues[14] found that admission TEG and ROTEM parameters available within 5 minutes of assay initiation more accurately predicted MT compared with the slower conventional coagulation assays (CCAs).

One difficulty in conducting MT research is that the traditional definition on which much of the literature is based ($\geq$10 PRBC units within 24 hours) is woefully inadequate: it does not capture the intensity of resuscitative efforts and is prone to survivor bias.[15] In particular, rapidly hemorrhaging patients are excluded when they exsanguinate before reaching the threshold, whereas less critically ill patients are included when they accrue units steadily over 24 hours. In response, newer definitions of MT that delineate use of blood products within a narrower timeframe have gained acceptance. For example, the concept of the critical administration threshold (CAT), defined as the transfusion of at least 3 PRBC units within any 1-hour time window within the first 24 hours,[16] has been prospectively validated in trauma subjects and found to be a more sensitive predictor of mortality than the traditional MT definition.[17] An advantage of CAT is that it can be obtained prospectively. Studies have shown that patients who reach CAT soon after presentation or who reach CAT multiple times have increased mortality,[16,17] and CAT may serve as an indicator to proceed with abbreviated instead of definitive laparotomy.[18]

PHARMACOLOGIC TREATMENT OPTIONS

The term damage control originated in the United States Navy to describe the protocol used to save a ship that has suffered catastrophic structural damage from sinking, placing a heavy emphasis on the limitation and containment of fires and flooding.[19] This term was adopted by trauma surgeons to describe the use of abbreviated surgeries to rapidly temporize life-threatening injuries (namely, hemorrhage) with delay of definitive repair until after adequate resuscitation. Damage control surgery is

associated with improved survival in severely injured trauma patients presenting with profound physiologic derangement[20,21] but is associated with several complications, including ventral hernias, surgical site infections, and increased ventilator dependence.[22]

DCR describes the resuscitation strategy that evolved in conjunction with damage control surgery. It represents a major paradigm shift away from the old days of resuscitation with isotonic crystalloids, followed sequentially by PRBCs, plasma, and finally platelets. Instead, DCR emphasizes the early use of plasma to not only restore volume but also correct major physiologic derangements, including hypoperfusion, shock, and coagulopathy. Major principles of DCR in the management of hemorrhagic shock include minimization of isotonic crystalloids, permissive hypotension, transfusion of a balanced ratio of blood products, and goal-directed correction of coagulopathy (**Box 3**).

Minimization of Crystalloid

Isotonic crystalloids

Before the advent of DCR, isotonic crystalloids were a major component of fluid therapy for patients presenting with traumatic hemorrhagic shock. In the 1980s, Shoemaker and colleagues[23,24] reported associations between increased cardiac output, oxygen delivery, and survival in critically ill surgical subjects. The replication of this finding in a prospective randomized trial[25] helped popularize the strategy of supranormal resuscitation, which used large boluses of isotonic crystalloids to drive cardiac output and oxygen delivery to supranormal levels. At about this time, damage control laparotomy was first described and also began gaining widespread use.[20,21] The combination of these 2 treatment modalities in severely injured trauma patients resulted in the inability to close the abdominal wall due to massive intestinal and retroperitoneal edema,[26] which often persisted well after hemorrhagic shock was corrected. In 2003, Balogh and colleagues[27] demonstrated an association between supranormal resuscitation and increased incidences of abdominal compartment syndrome, multiple organ failure, and mortality.

Later, investigators began taking a closer look at the consequences of aggressive fluid therapy in surgical patients.[28] For example, intracellular edema secondary to aggressive crystalloid infusion was found to disrupt many vital biochemical processes, including pancreatic insulin synthesis and secretion,[29] hepatocyte glucose metabolism,[30] and cardiac myocyte excitability.[31] A subsequent randomized trial of supranormal resuscitation failed to replicate Shoemaker's initial success.[32] Still other trials reported that subjects randomized to restricted intravenous fluid resuscitation after elective surgery experienced less postoperative ileus[33] and fewer cardiopulmonary and wound complications[34] compared with those who underwent standard fluid resuscitation. Additional observational studies demonstrated significant associations between large volumes of crystalloid and adverse outcomes, such as increased

Box 3
Components of damage control resuscitation

- Minimization of isotonic crystalloid
- Permissive hypotension
- Transfusion of a balanced ratio of blood products
- Goal-directed correction of coagulopathy

incidence of dilutional coagulopathy, acute respiratory distress syndrome (ARDS), MODS, extremity and abdominal compartment syndromes, and mortality, in severely injured trauma subjects.[35,36] Analysis of the PROMMTT dataset found that increasing crystalloid use was independently associated with moderate or severe hypoxemia.[37]

Although clinicians now recognize the significant complications associated with infusing large volumes of crystalloid in severely injured trauma patients, the safety of relatively small crystalloid volumes has also been questioned. A retrospective study of over 3,000 trauma subjects by Ley and colleagues[38] found that infusion of 1.5 L or greater of crystalloid in the emergency department was independently associated with increased mortality, although the investigators did not report or include the use of blood products in their analysis. A retrospective study of more than 1200 blunt trauma subjects dichotomized subjects into high (>500 mL) and low ($\leq$500 mL) groups based on infusion of prehospital crystalloid, and stratified subjects by presence of prehospital hypotension.[39] After propensity adjustment, including PRBC units transfused, the investigators reported that there was no difference in mortality in subjects with prehospital hypotension; however, greater than 500 mL prehospital crystalloid was associated with increased mortality (hazard ratio 2.5, 95% CI 1.3–4.9) and increased coagulopathy by admission international normalized ratio (odds ratio [OR] 2.2, 95% CI 1.0–4.9) in subjects without prehospital hypotension. Although it is clear that liberal infusion of crystalloid in trauma patients is harmful, it is interesting that any volume of crystalloid may cause harm or, at least, offer no benefit.

Hypertonic saline

The trauma community has long been interested in hypertonic saline (HTS) as an initial resuscitative fluid after traumatic hemorrhage. Several in vitro and animal studies have demonstrated benefits of initial HTS resuscitation, including brisk increases in mean arterial pressure and cardiac output,[40] improved microcirculatory flow by decreasing endothelial cell edema,[41] and favorable immunomodulatory effects.[42,43] In small randomized trials of trauma subjects presenting with hemorrhagic shock, initial resuscitation with HTS resulted in decreased proinflammatory and increased antiinflammatory markers.[44,45] The Resuscitation Outcomes Consortium (ROC) performed a multicenter randomized control trial investigating prehospital resuscitation with normal saline, HTS, or hypertonic saline dextran (HSD) for subjects with hemorrhagic shock.[46] After enrollment of 853 subjects, interim analysis demonstrated no mortality difference between groups and the trial was stopped early due to futility. Further analysis demonstrated that the hypertonic solutions, particularly HSD, resulted in worse coagulopathy on admission compared with prehospital resuscitation with normal saline.[47]

Enthusiasm for HTS has waned since publication of the ROC trial results. Based on these data, crystalloids, including HTS, have little role in the initial resuscitation of traumatic hemorrhagic shock. Plasma has become the preferred means of volume expansion in this patient population (see later discussion).

Permissive Hypotension

While caring for combat casualties during World War I, W.B. Cannon and colleagues[48] recognized that

> *Injection of a fluid that will increase blood pressure has dangers in itself. Hemorrhage in a case of shock may not have occurred to a marked degree because blood pressure has been too low and the flow too scant to overcome the obstacle offered by the clot.*

The goal of permissive hypotension is to maintain only the minimal blood pressure necessary to perfuse the vital organs. The rationale, which Cannon recognized a century ago, is that elevations in blood pressure before surgical hemostasis is achieved may compromise a tenuous clot and exacerbate blood loss. Much of the evidence for this practice comes from animal studies. In a swine model of uncontrolled hemorrhage, Sondeen and colleagues[49] demonstrated that there was a reproducible mean arterial blood pressure of 64 plus or minus 2 mm Hg at which the clot was popped and rebleeding occurred. A meta-analysis identified 9 animal studies that investigated hypotensive resuscitation after hemorrhage, all of which reported decreased mortality with a pooled relative risk of 0.37 (95% CI 0.33–0.71) in animals undergoing hypotensive fluid resuscitation compared with those undergoing normotensive resuscitation.[50]

Comparatively, there are fewer such studies in human subjects. Bickell and colleagues[51] published the first such study in 1994. They randomized 289 subjects after penetrating torso injury to standard fluid resuscitation, which was begun prehospital, or delayed fluid resuscitation, which was begun in the operating room. The investigators reported significantly improved survival in the delayed resuscitation group (70% vs 62%). However, subsequent studies have reported mixed results. In 2002, Dutton and colleagues[52] randomized 110 subjects with hemorrhagic shock in the emergency department to initial fluid resuscitation with high (100 mm Hg) and low (70 mm Hg) SBP goals and reported no mortality difference between groups. A multicenter pilot trial by ROC randomized 192 prehospital hypotensive trauma subjects to high (110 mm Hg) and low (70 mm Hg) SBP goals and reported improved 24-hour survival in the low SBP group after blunt trauma (97% vs 82%) but no difference after penetrating trauma (81% vs 81%).[53] Significantly, all of the randomized trials cited excluded patients with significant head injury.

The ideal target blood pressure for the initial resuscitation of hemorrhagic shock before definitive hemorrhage control remains unclear. There are currently no concrete recommendations from any of the leading trauma organizations. An open question is how low and for how long the blood pressure can be kept before the harm outweighs the benefit. Another consideration is the head-injured patient, for whom even a single episode of hypotension may substantially increase TBI-related morbidity and mortality.[54] Finally, previous studies used crystalloid to achieve blood pressure goals and there are currently little data regarding hypotensive resuscitation with blood products such as plasma. However, the available data suggest permissive hypotension is probably safe for short periods of time (in the absence of TBI) until definitive hemorrhage control can be achieved.

Optimal Transfusion of Blood Products

In the mid-seventeenth century, Richard Lower performed the first successful animal-to-animal blood transfusion when he demonstrated that a dog hemorrhaged nearly to the point of death could be completely restored by the transfusion of another dog's blood.[55] In the early nineteenth century, English obstetrician James Blundell performed the first successful human-to-human blood transfusion to save the life of a woman with postpartum hemorrhage.[56] However, several barriers, including infections secondary to lack of sterile technique, no understanding of the different blood types, and catheter thrombosis due to deficient knowledge of anticoagulants, made blood transfusion prohibitively dangerous and difficult. It was not until the early twentieth century when these barriers were overcome that blood transfusions could become routine. For the next 50 years, transfusion of whole blood was the norm. By the 1970s, however, component therapy had replaced whole blood transfusions

to maximize the efficient utilization of donated blood and to limit the spread of blood-borne pathogens.

Plasma

Early definitive hemorrhage control and MT with DCR are the preferred treatment of the trauma patient in severe hemorrhagic shock. The actual composition of an MTP has changed drastically over the last 20 years. Before the advent of DCR, a trauma patient undergoing MT would have received stepwise resuscitation with crystalloid, artificial colloids, and PRBCs. Not until 1 to 2 blood volumes have already been replaced would plasma and platelets be given.[57] This all changed after the shift to DCR, which began in earnest with the landmark study by Borgman and colleagues[58] in 2007, a retrospective study of 246 massively transfused military trauma subjects treated at a US combat support hospital in Iraq. The investigators separated subjects into 3 groups by ratio of plasma to PRBC: low (median ratio 1:8), medium (median ratio 1:2.5), and high (median ratio 1:1.4). The all-cause mortality for the 3 groups were 65%, 34%, and 19%, respectively, whereas the mortality due to hemorrhage were 93%, 78%, and 37%, respectively. Every 1 unit increase in the ratio of plasma to PRBC was associated with an OR of 8.6 (95% CI 2.1–35.2) improved likelihood of survival. The same year, Johansson and colleagues[59] demonstrated that early transfusion of high ratios of plasma and platelets in subjects who underwent repair of a ruptured abdominal aortic aneurysm had significantly improved 30 day survival (66% vs 44%) compared with historical controls.

Further observational data describing the benefit of early high plasma ratios followed for civilian trauma patients.[60–63] In particular, the PROMMTT study was a multicenter prospective observational trial that analyzed 905 bleeding trauma subjects who received at least 1 PRBC unit within 6 hours, at least 3 PRBCs units within 24 hours, and survived for at least 30 minutes after arrival.[4] PROMMTT demonstrated that early utilization of higher ratios of plasma and platelets to PRBCs was associated with decreased in-hospital mortality. Specifically, every unit increase in the plasma to PRBC and platelet to PRBC ratios within the first 6 hours (when hemorrhage was the primary cause of death) was associated with an adjusted hazard ratio of 0.31 (95% CI 0.16–0.58) and 0.55 (95% CI 0.31–0.98) of in-hospital mortality, respectively. After the first 24 hours when other causes of death increased in incidence, ratios of plasma and platelets to PRBCs were no longer significantly associated with mortality.

The first randomized control trial investigating the optimal ratio of blood products was the Pragmatic, Randomized Optimal Platelet and Plasma Ratios (PROPPR) study, a multicenter study that randomized 680 severely injured, bleeding trauma subjects to resuscitation with a 1:1:1 or 1:1:2 ratio of plasma, platelets, and PRBC.[5] The investigators found no differences in 24-hour or 30-day mortality. However, subjects in the higher plasma and platelets ratio (1:1:1) group had significantly increased achievement of hemostasis (86% vs 78%) and decreased death due to bleeding (9% vs 15%) compared with the low ratio (1:1:2) group. Other studies have demonstrated improved subject outcomes after implementation of DCR principles. Shrestha and colleagues[64] have shown increased likelihood of successful nonoperative management and survival in civilian subjects with high-grade liver injuries after blunt trauma. In the military setting, soldiers injured in combat are also surviving with more severe injuries after implementation of DCR.[65] Based on these studies, the ACS TQIP Massive Transfusion in Trauma Guidelines recommend DCR in patients who meet MTP triggers (**Box 4**).[66]

The underlying mechanism behind these benefits, however, is unclear. Restoration of intravascular volume and correction of coagulopathy are clearly important aspects.

Box 4
If massive transfusion protocol (MTP) trigger criteria are met, initiate damage control resuscitation (DCR)

- Begin universal blood product infusion rather than crystalloid or colloid solutions.
- Transfuse universal red blood cells (RBCs) and plasma in a ratio between 1:1 and 1:2 (plasma/RBC).
- Transfuse 1 single donor apheresis or random donor platelet pool for each 6 units of RBC.
- Blood products should be automatically sent by the transfusion service in established ratios.
- Subsequent coolers should be delivered at 15-minute intervals until the MTP has been terminated.
- The goal is to keep at least 1 MTP cooler ahead for the duration of the MTP activation.

Adapted from ACS TQIP. Massive Transfusion in Trauma Guidelines. American College of Surgeons. Available at: https://www.facs.org/%7E/media/files/quality%20programs/trauma/tqip/massive%20transfusion%20in%20trauma%20guildelines.ashx. Accessed April 13, 2016.

In animal models of hemorrhagic shock, plasma-based resuscitation mitigated hyperfibrinolysis[67] and platelet dysfunction[68] compared with crystalloid resuscitation. However, proteins involved with coagulation represent only a small fraction of the human plasma proteome. Besides restoration of intravascular volume and clotting factors, another benefit is likely repair of endothelial injury. Severe trauma,[69] as well as several other inflammatory conditions, including diabetes,[70] sepsis,[71] and ischemia-reperfusion,[72] are known to result in injury to the endothelium with loss of microvascular integrity, resulting in extravasation of intravascular fluid into the interstitial space. Liberal resuscitation with crystalloids and artificial colloids increases hydrostatic pressure without repairing the endothelial injury, resulting in edema and the edema-related complications that were common in the pre-DCR era (**Fig. 1**). In contrast, in vitro[73–75] and animal models[76,77] of hemorrhagic shock demonstrate that plasma restores microvascular integrity, in part by repair of the endothelial glycocalyx layer (EGL). In a large animal model of concomitant hemorrhagic shock and TBI, resuscitation with fresh frozen plasma (FFP) resulted in less secondary brain injury compared with resuscitation with crystalloid or artificial colloid, likely secondary to restoration of cerebral endothelium.[78] In trauma patients, there are strong correlations between increasing circulating levels of glycocalyx components (a marker for EGL injury) and trauma severity, coagulopathy, and mortality,[69,79,80] although it remains unclear if these relationships are causative or merely associative.

Clinicians have long recognized that time is against the bleeding trauma patient and that faster initiation of lifesaving interventions improves outcomes. In light of this, key logistical hurdles must be overcome to expedite the delivery of plasma. Blood banks stock FFP, which has a shelf of life of up to 1 year at −18°C but requires 20 to 30 minutes of thaw time before use, limiting immediate availability. Options to make plasma readily available for emergency use include stocking thawed plasma and liquid plasma. After FFP is thawed, the most labile clotting factors (V and VIII) maintain 65% of their activity at the end of its 5 day shelf life.[81] Liquid plasma, on the other hand, is never frozen and includes a preservative to maintain stability of most clotting factors for up to 26 days. Toward the end of its shelf life, most clotting factors maintain 88% activity and in vitro studies demonstrate that never-frozen liquid plasma has a better coagulation profile than thawed plasma.[82]

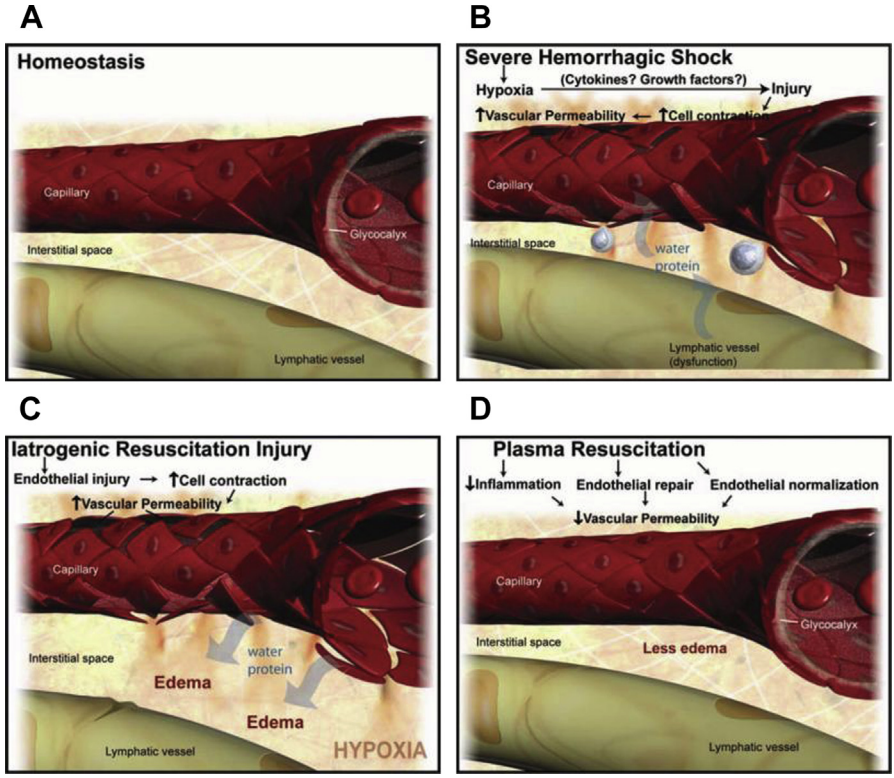

Fig. 1. Proposed effect of hemorrhagic shock and crystalloid versus plasma resuscitation on the microvasculature. (*A*) Homeostasis before injury. (*B*) Hemorrhagic shock results in shedding of endothelial glycocalyx layer (EGL) components, resulting in endothelial injury, microvascular permeability, and leakage of fluid into the interstitial space. (*C*) Crystalloids increase hydrostatic pressure in the presence of persistent endothelial injury, resulting in edema. (*D*) Plasma restores intravascular volume while restoring the EGL and repairing endothelial injury, limiting edema. (*From* Pati S, Matijevic N, Doursout MF. Protective effects of fresh frozen plasma on vascular endothelial permeability, coagulation, and resuscitation after hemorrhagic shock are time dependent and diminish between days 0 and 5 after thaw. J Trauma 2010;69(Suppl 1):S61; with permission.)

Another logistical hurdle affecting speed of delivery is storage location. For example, a before-and-after study demonstrated that moving 4 units of universal-donor thawed plasma from the blood bank to the emergency department was independently associated with decreased time to first plasma transfusion, decreased usage of PRBCs (coefficient −2.9, 95% CI −5.7 to −0.2) and plasma (coefficient −2.7, 95% CI −5.4 to −0.1) within the first 24 hours, and decreased mortality (OR 0.43, 95% CI 0.19–0.96).[83] The multicenter PROPPR study demonstrated the feasibility of high-level trauma centers to rapidly deliver universal donor plasma to hemorrhaging trauma patients quickly and consistently with minimal wastage.[84]

In the last several years, many investigators have proposed transitioning hospital interventions for trauma patients to the prehospital phase of care, including plasma. A retrospective study that analyzed 1677 severely injured trauma patients who were transported by helicopter found that in-flight plasma transfusion was associated

with improved acid-base status on arrival and decreased overall transfusion of blood products within the first 24 hours.[85] Although there was no mortality benefit in all patients, prehospital plasma transfusion was associated with decreased mortality in the most critically ill patients (those admitted directly to the intensive care unit, interventional radiology, operating room, or morgue). Randomized trials to study the impact of prehospital plasma in ground[86] and aeromedical transport[87] are on-going.

A final logistic consideration is that individuals with the universal plasma donor AB blood type make up only 4% of the population of the United States.[88] The scarcity of AB plasma has been further exacerbated by the widespread adoption of DCR principles. To circumvent this shortage, the use of type A plasma has been proposed as an alternative. The rationale is that (1) 85% of individuals in the United States have either type A or type O blood,[88] making type A plasma compatible with the almost all potential recipients; (2) the plasma transfused with type O apheresis platelets is routinely given to type-incompatible recipients with hemolytic reactions occurring very rarely[89,90]; (3) laboratory examination of male type A plasma units found predominantly low titers of anti-B[91]; and (4) the risk of transfusion-related acute lung injury (TRALI) is currently much higher with type AB plasma than type A.[92] Based on limited retrospective data, the emergency use of type A plasma seems safe.[93–95] As this practice becomes widespread,[96] more accurate data about the safety profile of this practice will soon become available.

Previous studies had raised concerns regarding the safety of increased plasma use, citing potentially increased risk of developing inflammatory complications such as TRALI, ARDS, and MODS.[97–99] Analysis of the prospectively acquired PROMMTT dataset did not demonstrate an independent association between blood product use and moderate-to-severe hypoxemia.[37] Indeed, the PROPPR randomized trial found no difference in inflammatory or transfusion-related complications between the high-ratio and low-ratio groups.[5]

Platelets

The inclusion of platelets with a balanced MTP approach is intuitive to more accurately mimic the whole blood that was lost. Retrospective studies[60,100,101] report increased survival in massively transfused patients who received high ratios of platelets to PRBCs. PROMMTT provided prospective observational data demonstrating that every unit increase in the platelet to PRBC ratio decreased the hazard ratio of mortality within the first 6 hours by 0.55 (95% CI 0.31–0.98).[4] As was the case with plasma, this relationship parallels the risk of death from hemorrhage and became weaker with time, such that the platelet to PRBC ratio after 24 hours was no longer significantly associated with mortality. In the PROPPR randomized trial,[5] subjects in the high plasma and platelets ratio group had lower death due to hemorrhage, although the independent effects of plasma and platelets cannot be disentangled in this study. The most recent guidelines from the ACS Committee on Trauma recommend transfusing 1 unit of platelets (what was previously known as a 6-pack of platelets) for every 6 PRBC units.[102]

Fresh whole blood

Fresh whole blood (FWB) can be stored at room temperature for up to 8 hours and at 6°C of less for 24 to 48 hours, depending on institutional guidelines.[103] Although economic and other considerations have all but eliminated the civilian use of FWB, several factors make FWB an attractive option for the resuscitation of hemorrhagic shock. First, the diluting effect secondary to the anticoagulants and additives in each blood product component reduces the hematocrit, factor activity, and platelet count of a

1:1:1 ratio of component therapy compared with a unit of FWB (**Table 1**).[104] An in vitro study compared the parameters of FWB and reconstituted whole blood (1:1:1 ratio component therapy) and reported findings similar to the theoretic calculations.[105] Second, the use of FWB would preclude the loss of quality of blood product components due to storage time.[106–108] Indeed, use of blood products with increased storage duration is associated with increased mortality and morbidity.[109–111] Third, use of FWB would reduce the number of donors to which the recipient is exposed and may reduce the risk of blood-borne pathogens. Finally, transfusion of 1 whole blood unit is logistically simpler than transfusion of multiple components and may reduce harm from administrative errors.

The limited availability of refrigeration and potential shortages of blood product components means that FWB will always have a niche in the austere environment. Military experience with the transfusion of FWB is extensive, dating as far back as World War I, and includes the transfusion of over 9000 whole blood units during the recent military conflicts in Afghanistan and Iraq.[112] Two retrospective analyses of combat casualties treated at a combat support hospital[113] and by forward surgical teams[114] reported improved survival in patients who received FWB compared with component therapy (PRBC and FFP only, no platelets due to a shortage). Lingering questions regarding the use of FWB include warm versus cold storage, shelf life, and the ability to rapidly screen FWB units for infectious agents and type compatability,[103] although some have advocated the use of low anti-A/B titer type O whole blood as an alternative to type specificity.[115]

Establishing the ability to rapidly and safely transfuse FWB for trauma patients requires changes to donor blood processing at regional blood banks. Donor whole blood could be theoretically held for its shelf life (24–48 hours) and subsequently processed into components if not transfused as FWB. The authors recently performed a pilot study that demonstrated the feasibility of modified whole blood therapy in a civilian trauma setting[116]; however, the whole blood units used in the study were leukoreduced and platelet-poor, meaning patients still required transfusions of apheresis platelets.

Goal-directed correction of coagulopathy

Perturbations of different aspects of TEG and ROTEM tracings point to deficiencies in different components of coagulation, and this allows using blood products or other adjuncts to correct these deficiencies in a targeted manner. The use of TEG and ROTEM in liver transplantation[117] and cardiac surgery[118] has been shown to reduce blood product use with similar or improved patient outcomes. In the case of the relatively stable trauma patient, in whom surgical hemorrhage control is achieved and MTP is deactivated, the use of TEG and ROTEM to guide further blood product utilization is intuitive and an important component of DCR.[57] A recent single-institution

Table 1
Calculated parameters of fresh whole blood versus reconstituted whole blood with 1 packed red blood cell unit (335 mL with hematocrit of 55%), 1 platelet unit (5.5×10^{10} platelets in 50 mL), and 1 fresh frozen plasma unit (80% coagulation factor activity)

	Fresh Whole Blood	1:1:1 Component Therapy
Hematocrit (%)	38–50	29
Platelets ($\times 10^9$/L)	150–400	88
Coagulation factor activity (%)	100	65

randomized controlled trial (n = 111) reported that use of a goal-directed, TEG-guided MTP compared with MTP guided by CCAs to resuscitate severely injured patients was associated with improved survival (11/56 deaths TEG vs 20/55 deaths CCA, $P = .049$).[66] Data regarding the use of blood products and other therapeutics in response to abnormalities of different TEG/ROTEM parameters, are presented elsewhere in this issue.

However, the role of coagulation assays to guide transfusion of blood products during MTP in lieu of fixed ratios is unclear and controversial.[119,120] Although it was not designed to answer this question, analysis of data from the PROPPR randomized trial demonstrated subjects randomized to the low (1:1:2) plasma and platelet ratio group were transfused additional units of plasma and platelets in a laboratory-driven, goal-directed fashion after MTP was deactivated, such that the cumulative ratio of blood products used approached 1:1:1 by 24 hours,[5] suggesting that the optimal ratio may be close to 1:1:1 regardless of how it is arrived at. Direct comparisons between fixed ratio versus goal-directed MTP are lacking in the literature,[121,122] although other investigators argue that the 2 strategies are not mutually exclusive.[123]

TREATMENT RESISTANCE AND COMPLICATIONS

Cryoprecipitate and Fibrinogen Concentrate

Cryoprecipitate, collected as the precipitate of plasma after a freeze-thaw cycle, is enriched in factors VIII and XIII, von Willebrand factor, fibronectin, and fibrinogen. These factors are theoretically replaced at physiologic levels by plasma during the course of MT, and the discussion regarding the use of cryoprecipitate focuses on the need for additional boluses of these components, particularly fibrinogen. Although previous data suggested a critical fibrinogen threshold of 100 mg/dL (1.0 g/L), more recent studies found significant bleeding at this level,[124,125] indicating the need for a higher cutoff. Currently, the ACS Committee on Trauma recommends transfusing cryoprecipitate to maintain fibrinogen at 180 mg/dL or greater,[102] whereas European guidelines describe a minimum cutoff of 150 to 200 mg/dL.[126]

An analysis of blood samples from 52 massively transfused patients found that fibrinogen was commonly the first factor to reach critically low levels.[127] A review of 1332 massively transfused combat casualties found that use of cryoprecipitate within the first 24 hours was independently associated with improved survival.[128] These data suggest a potential benefit with early delivery of fibrinogen, either by fibrinogen concentrate (off-label use in the United States) or cryoprecipitate. A randomized controlled trial to evaluate the use of prehospital fibrinogen concentrate (Fibrinogen in Trauma-induced coagulopathy [FlinTIC])[129] is ongoing.

Continued Hemorrhage

Continued hemorrhage despite adequate surgical control and DCR is secondary to worsening trauma-induced coagulopathy. Although DCR is designed to treat coagulopathy directly, adjunctive measures may also be used. We defer discussion of treatment of coagulopathy, in this issue.

Transfusion-Related Acute Lung Injury

The most notable complication resulting from blood product transfusion is TRALI, characterized by inflammatory-mediated pulmonary edema resulting in hypoxia within hours of transfusion.[130] Although any blood product may precipitate TRALI, the risk was historically highest with plasma.[92] Recognizing that a significant source of TRALI cases were precipitated by plasma donated by multiparous women who likely

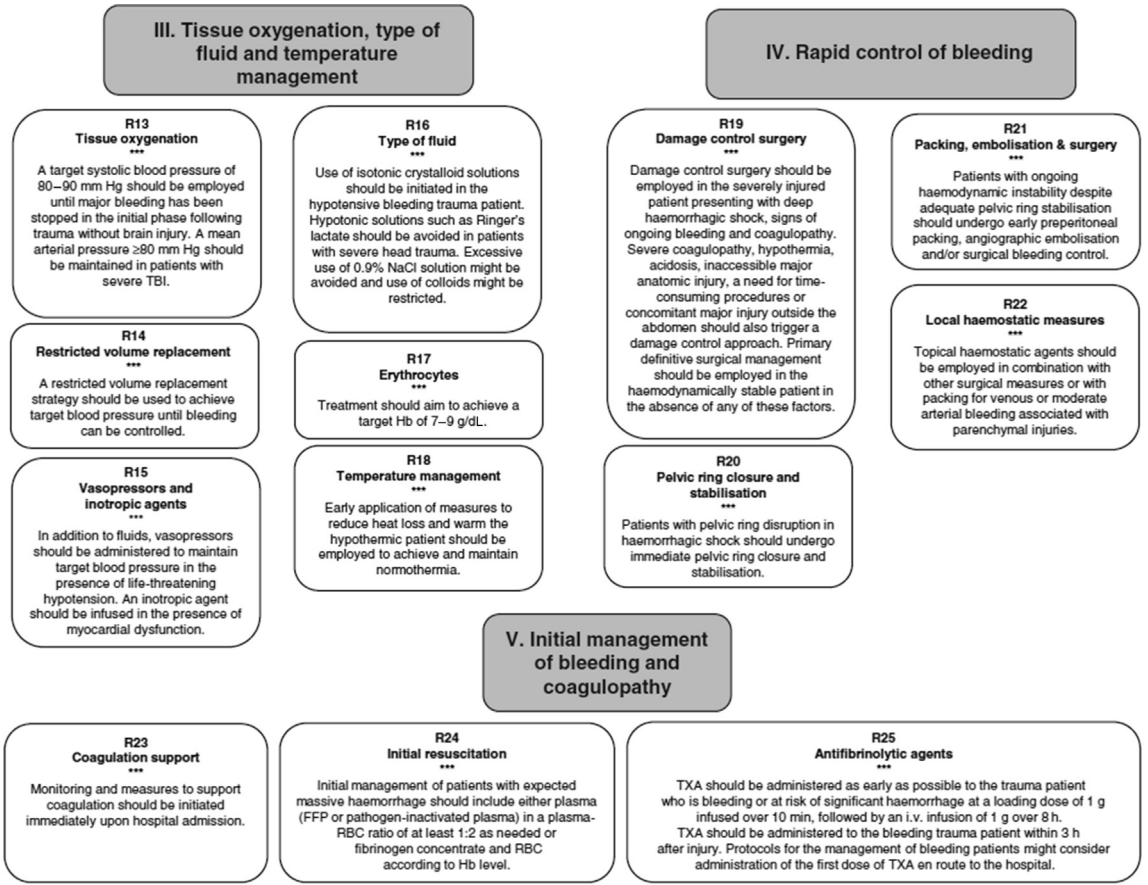

Fig. 2. Summary of treatment modalities for the bleeding trauma patient. (*Adapted from* Rossaint R, Bouillon B, Cerny V, et al. The European guideline on management of major bleeding and coagulopathy following trauma: fourth edition. Crit Care 2016;20:100.)

developed alloantibodies after becoming sensitized during pregnancy, initiatives were introduced in 2006 to reduce the incidence of TRALI.[92] This included screening programs and preferentially using plasma from male donors for transfusion. After implementation of these initiatives, the American Red Cross reported that the incidence of TRALI decreased from 18.6 cases per million plasma units transfused to 4.2 cases per million, no different from the TRALI risk associated with PRBC.[92] An exception is type AB plasma; due to its scarcity, a substantial proportion of transfused AB plasma continues to come from female donors. As a result, the incidence of TRALI associated with AB plasma has remained constant. Currently, the risk of TRALI after transfusion of AB plasma carries an OR of 14.5 (95% CI 6.8–30.9) compared with other plasma types,[92] which has been cited as a rationale for the transition to type A plasma for emergency use.

SUMMARY

One of the most important lessons of the last 20 years is that the choice, timing, and volume of resuscitation fluid for the trauma patient has as much impact on outcome as operative treatment of the tissue injuries. The advent of DCR was a breakthrough in trauma care. Crystalloids now have little role in the initial resuscitation of traumatic hemorrhagic shock, and plasma is the preferred means of volume expansion after traumatic hemorrhagic shock. The ACS Committee on Trauma (see **Box 4**)[102] and European Task Force for Advanced Bleeding Care in Trauma (**Fig. 2**)[126] recommend using a ratio of plasma to PRBC of at least 1:2 for the initial resuscitation of hemorrhaging trauma patients, whereas the National Institute for Health and Care Excellence in the United Kingdom recommends a 1:1 ratio.[131] At this stage, the use of plasma is quite low-risk compared with its potential benefits. The authors emphasize again that replacement of volume and clotting factors is likely only part of the story of plasma, and research efforts are on-going to identify the specific mechanisms underlying its benefits.

Although much has been learned since the pre-DCR days, many questions remain. What are the roles of whole blood and prehospital transfusion, as well as the safety of uncrossmatched type A plasma for emergency use? Rather than the use of fixed transfusion ratios, can improvements in diagnostics and therapeutics enable precise, targeted correction of coagulopathy and hypoperfusion during MT? Improvements in trauma care have historically arisen out of armed conflict but randomized trials run by multicenter research consortiums have enabled a new generation of physician-scientists to produce high-level evidence outside of the theater of war in an effort to answer these questions. With increasing collaboration across multiple centers and specialties, understanding in this challenging area of medicine will be furthered.

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