Hypovolemic Shock Resuscitation

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KEYWORDS

• Hemorrhagic shock • Septic shock • Massive transfusion • Blood loss • Crystalloid

KEY POINTS

- Hypovolemic shock is defined as inadequate tissue perfusion caused by decreased intravascular circulating volume.
- Early transfusion with a 1:1:1 ratio of fresh frozen plasma to platelets to packed red blood cells has been associated with improved outcomes in patients requiring massive transfusion.
- Monitoring coagulation function with thromboelastography or rotational thromboelastometry may be superior to conventional coagulation assays in patients with hypovolemic shock.

DEFINITION OF SHOCK

Shock is the inability of the body to maintain adequate end-organ perfusion. Hypovolemic shock caused by blood loss is frequently encountered after severe injury.[1] Hemorrhagic shock should be assumed to be the cause of hypotension in all trauma patients until proven otherwise. Shock is a strong predictor of mortality, and is a major risk factor for the development of complications, particularly multiple organ dysfunction. Hence, it is important to rapidly identify patients in shock so that appropriate resuscitation can begin as soon as possible. Indicators of shock include elevated heart rate, low blood pressure, narrowed pulse pressure, decreased capillary refill, cool clammy extremities, pale skin, increased skin turgor, low urine output, dry mucus membranes, and alterations in mental status. In certain patients, clinicians must keep in mind that significant blood loss can occur with little effect on vital signs. In particular, pediatric patients have excellent cardiovascular reserve, preventing a drop in blood pressure even in the presence of large volume blood loss. Conversely, elderly patients are often unable to mount a tachycardic response to hemorrhage, or may be on medications that blunt or prohibit normal response to blood loss. Elderly patients often also

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have chronic underlying hypertension, and apparently normal blood pressure may, for them, be relative hypotension.

CLASSIFICATION OF HEMORRHAGIC SHOCK

Hemorrhagic shock is classified according to severity from class I to IV shock (**Table 1**). Class I shock is minor blood loss, often resulting in no significant derangement of vital signs or findings on clinical examination. Severity increases with increasing volumes of blood loss, with class IV shock caused by loss of more than 40% of circulating blood volume and resulting in hypotension, tachycardia, and severe multisystem organ derangements.

MASSIVE BLOOD LOSS AND MASSIVE TRANSFUSION

In addition to the traditional classifications of shock, a subset of patients with extensive injuries causing rapid hemorrhage develop massive blood loss (MBL) (**Box 1**). These patients often require alterations in goals of care from definitive management to damage control, and may require different resuscitation strategies and monitoring. Patients with MBL often require massive transfusion in response to their hemorrhage. Massive transfusion (MT) is typically defined as 10 or more units of packed red blood cells (PRBCs) in a 24-hour period.[2–7] At this level of transfusion, hemodilution of fibrinogen, platelets, and clotting factors can occur as whole blood continues to be lost, and is replaced with only crystalloid or PRBCs. These patients are at high risk for developing acidosis and hypothermia from blood loss, injury burden, and associated need for multicavitary surgery. This acidosis and hypothermia can further exacerbate coagulopathy, resulting in the "bloody vicious triad."[8]

Of all trauma admissions, 8% to 11% of patients will require a blood transfusion during their hospital stay.[5] Only approximately 3% of trauma patients will have blood loss requiring MT, although this percentage may increase to 8% to 15% among busy urban trauma centers and among military casualties.[9–13] As many as 24% of patients presenting in shock will require MT, and those with MT account for up to 60% to 70% of all PRBCs used.[14,15] Mortality increases in a linear fashion with PRBC transfusions and can be as high as 60% to 100% (**Table 2**).[3,9,13–19]

CLASSICAL RESUSCITATION OF SHOCK STATES

The most important step in resuscitation of hemorrhagic shock is identification and rapid control of the source of bleeding, which can be accomplished with direct pressure, application of a tourniquet, suture ligation, or surgery. Although maneuvers to

Table 1
Classes of hemorrhagic shock

	Class I	Class II	Class III	Class IV
Blood loss (mL)	≤750	750–1500	1500–2000	≥2000
Blood loss (% blood volume)	≤15%	15%–30%	30%–40%	≥40%
Pulse rate (BPM)	<100	>100	>120	>140
Blood pressure	Normal	Normal	↓	↓
Pulse pressure	Normal or ↑	↓	↓	↓
Capillary refill	Normal	Delayed	Delayed	Delayed

Abbreviation: BPM, beats per minute.

Box 1
Definitions of massive blood loss

Loss of entire blood volume within 24 hours

Loss of 50% of blood volume within 3 hours

Ongoing blood loss of 150 mL/min

Ongoing blood loss of 1.5 mL/kg/min

Rapid blood loss leading to circulatory failure

Data from Fraga GP, Bansal V, Coimbra R. Transfusion of blood products in trauma: an update. J Emerg Med 2010;39(2):253–60.

control bleeding are ongoing, attempts should be made to ensure adequate intravenous access, which can be accomplished by placing 2 large-bore peripheral intravenous lines, or an intraosseous or central line.

Once access is secured, resuscitation should begin with immediate infusion of warmed fluids to restore circulating blood volume replacing losses from hemorrhage. Classical resuscitation strategies for hemorrhagic shock, taught by Advanced Trauma Life Support (ATLS), suggest bolus infusion of 2 L of warmed crystalloid if hypotension is present, followed by replacement of ongoing fluid or blood losses with isotonic fluids in a 3:1 ratio to accommodate losses into the interstitial space.[1,20]

Choice of fluid for resuscitation is an area of ongoing research. Resuscitation fluids should be considered medications, and as with any medication, may be associated with deleterious side effects, including exacerbation of cellular injury, immunosuppression, and inflammation.[20–22] Resuscitation fluids may result in significant acid base and electrolyte derangements. The ideal resuscitation fluid should be cheap, safe, easy to store, and portable; increase oxygen carrying capacity; have beneficial immuno-inflammatory properties; and be able to rapidly and effectively increase intravascular volume.

Crystalloids

Normal saline and lactated Ringer solution are the most commonly used resuscitation fluids in hypovolemic and hemorrhagic shock. Although lactated Ringer solution may theoretically be preferable because of its ability to buffer metabolic acidosis and prevent hyperchloremic acidosis associated with normal saline infusions, this

Table 2
Stepwise increase in mortality with transfusion

	Mortality		
PRBCs (Units)	Como et al,[15] 2004	Huber-Wagner et al,[17] 2007	Inaba et al,[142] 2008 *Uncross-Matched
1–10	22%	14.8%	<7 = 30% >7 = 54%
11–20	30%	35.1%	<15 = 78% >15 = 95%
21–40	50%	20–29 = 53.7% ≥30 = 60.4%	
>40	59%		

* This study includes patients given uncross-matched blood.

beneficial effect is seen only with massive infusions. Studies comparing normal saline and lactated Ringer solution in minimal and moderate hemorrhage show equivalent outcomes.[1,23,24] Because of its composition, a theoretical risk of hyperkalemia is associated with the use of lactated Ringer solution, which may be exacerbated in patients with acute kidney injury or chronic renal insufficiency. Additionally, the D isomer of lactate may have adverse inflammatory and immunomodulatory properties.[1,23]

Colloids

Colloids are theoretically retained in the intravascular space to a greater extent than crystalloids, which may have several benefits during resuscitation. First, intravascular volume can be expanded more rapidly. Second, a smaller total volume of fluid may be used to achieve adequate perfusion. Third, because there is potentially less third-spacing, the risk of complications such as bowel edema, abdominal compartment syndrome (ACS), and acute respiratory distress syndrome (ARDS) may be decreased. However, numerous studies examining the use of colloids in resuscitation of the critically ill and injured have failed to demonstrate a statistically significant benefit. A Cochrane review in 2002 comparing albumin with crystalloid resuscitation among a mixed intensive care unit (ICU) population found that the relative risk (RR) of death was higher with albumin than the comparison group (RR, 1.52; CI, 1.17–1.99), with a 5% absolute increase in the overall risk of death (14% compared with 9%).[25]

The Saline versus Albumin Fluid Evaluation (SAFE) Study, the largest randomized controlled trial to date, compared 3497 patients who received 4% albumin with 3500 patients receiving normal saline and found no significant difference in mortality, days on the ventilator, need for renal replacement therapy, or hospital length of stay.[26] Subsequent meta-analyses that included the SAFE Study have confirmed overall equivalence in outcomes when comparing albumin with crystalloid for hypovolemic critically ill patients.[27,28] Given the relative expense and lack of beneficial effects, albumin as a primary resuscitation fluid cannot be recommended. One should also keep in mind that some patients may be harmed by albumin resuscitation. A subgroup analysis of patients with traumatic brain injury (TBI) in the SAFE Study found that albumin resulted in significantly higher mortality in these patients (RR, 1.63; CI, 1.17–2.26; $P = .003$). This risk was even more pronounced among patients with severe TBI (RR, 1.88; CI, 1.31–2.7; $P<.001$).[29] Increased mortality associated with albumin resuscitation has also been noted in trauma and burn patients.[26,28,29]

In addition to albumin, multiple trials of synthetic colloids have also been conducted, including a variety of hydroxyethyl starch formulations. Synthetic colloids are appealing as a resuscitation fluid because they can be manufactured cheaply, avoid risks of blood borne pathogens, and theoretically increase circulating blood volume to a greater extent than crystalloids. However, significant evidence shows that their use may be associated with coagulopathy and an increased risk of acute kidney injury. Animal studies demonstrate significantly increased bleeding and clinical coagulopathy with hydroxyethyl starch compared with albumin and blood products. Even more concerning is that the coagulopathy in these animals manifested as increased bleeding and hemorrhagic death but was not associated with derangements in traditional laboratory measures of clotting, such as prothrombin time (PT) and activated partial thromboplastin time (aPTT).[30–32] Meta-analysis of both in vitro and in vivo studies involving several hydroxyethyl starch formulations confirmed these results, finding significant hypocoagulatory effects of hydroxyethyl starch as measured by thromboelastography (TEG) or rotation thromboelastometry (ROTEM).[33] Multiple meta-analyses have confirmed the association between acute kidney injury and hydroxyethyl starch administration with odds ratios for acute kidney injury ranging from 1.5–1.92.[34,35]

This association seems particularly strong when hydroxyethyl starch is used in resuscitating patients with sepsis and septic shock.[34]

Among humans, a meta-analysis of hydroxyethyl starch compared with other resuscitation fluids found no significant difference in mortality with the use of hydroxyethyl starch, but found insufficient data to determine overall affect of hydroxyethyl starch on coagulopathy and acute kidney injury.[36] A randomized controlled trial of severely injured trauma patients comparing hydroxyethyl starch and normal saline found that patients given hydroxyethyl starch required significantly more blood transfusions; however, they were also more severely injured. No difference in mortality was found between the groups.[37] A retrospective review of 2225 trauma patients found that those who received hydroxyethyl starch were more likely to develop acute kidney injury (RR, 1.73; CI, 1.3–2.28). Hydroxyethyl starch was also associated with increased risk of mortality (RR, 1.84; CI, 1.48–2.29) and was an independent predictor for death.[38]

HYPERTONIC SALINE

Hypertonic saline has anti-inflammatory and laudable immunomodulatory effects in animal models of hemorrhagic shock. These animal models demonstrate decreased lung and intestinal injury after hypertonic saline resuscitation.[21,22,39] Similar anti-inflammatory effects are also seen in small human trials.[39] In trauma patients, hypertonic saline has the additional benefit of acting as an osmotic agent to decrease cerebral edema in patients with TBI.[40,41] Because hypertonic solutions are retained more in the intravascular space, they have the potential to decrease risks of ACS and ARDS. Unfortunately, human clinical trials to date have not consistently found a benefit to hypertonic saline over isotonic fluids in the prehospital or acute resuscitation phase after traumatic injury.[42–45] Although an analysis of blunt trauma patients receiving hypertonic saline in conjunction with MT showed an improvement in ARDS-free survival (HR, 2.18; CI, 1.09–4.36),[42] a larger follow-up multicenter randomized controlled trial in trauma patients with hypovolemic shock found no survival or morbidity benefit compared with normal saline.[43] Subgroup analysis also revealed significantly increased mortality among the subset of patients who did not require a blood transfusion in the first 24 hours.[43] Additional studies of trauma patients with TBI also failed to demonstrate any improvement in mortality or neurologic outcomes.[46,47]

Blood Products

ATLS suggests transfusion of PRBCs only if patients fail to respond to crystalloid bolus.[48] Use of blood components, such as fresh frozen plasma (FFP), platelets, and fibrinogen, were not classically part of the initial trauma resuscitation. These components were typically only given if laboratory evidence of deficiencies were noted during ongoing resuscitation. Classical triggers of component therapy include FFP transfusion for PT and aPTT greater than 1.5 to 1.8 times normal; platelet transfusion for platelets less than 50×10^9/L; and cryoprecipitate transfusion if fibrinogen less than 0.8 g/L.

DAMAGE CONTROL RESUSCITATION

Problems with Classical Resuscitation

Classical resuscitation strategies present several problems in patients with hemorrhagic shock after trauma. First, immediate fluid resuscitation to normal goal blood pressures may increase the blood flow to injuries and perfusion pressures, increasing the risk of "popping the clot," causing recurrent bleeding, or increasing ongoing blood loss.[49] Additionally, the large volumes of fluid given in aggressive resuscitation strategies may result in significant third-spacing, causing complications such as bowel

edema and anastomotic leaks, ACS, and ARDS.[50,51] Classical resuscitation strategies also presume that coagulopathy is a late complication after trauma. However, several studies have challenged this paradigm and demonstrated that coagulopathy is present in up to 24% to 74% of patients on admission.[4,5,52–57] Far from treating or preventing this complication, traditional resuscitation strategies may exacerbate bleeding through inducing a dilutional coagulopathy and exacerbating hypothermia. Several studies show a stepwise increase in coagulopathy associated with the volume of crystalloid administered.[6,54] Good evidence also suggests that resuscitation of MBL with PRBCs alone results in significant derangements of coagulation and thrombocytopenia as PRBC replacement approaches 12 units, or one circulating blood volume.[58,59] Even in the absence of documented coagulopathy, patients with MBL or requiring MT have poor outcomes in response to classic resuscitation strategies, with mortality ranging from 36% to 62%; this increases to 46% to 77% when coagulopathy is present.[7,53,60–62] Because of the potential for exacerbation of coagulopathy, increased bleeding, and potential complications associated with classical resuscitation, newer "damage control resuscitation strategies" are proposed. Damage control resuscitation (DCR), similar to damage control laparotomy, applies to patients with overwhelming injury burden and MBL. The tenets of DCR include selective use of permissive hypotension, early aggressive use of blood transfusions in a 1:1:1 ratio of PRBCs to FFP to platelets, and selective use of hemostatic adjuncts. The goals of DCR are to minimize bleeding, increase end organ perfusion, prevent coagulopathy, and minimize risks of multisystem organ dysfunction.

Permissive Hypotension

Permissive hypotension strategies withhold or minimize fluids as long as cerebral perfusion is evident and systolic blood pressures remain above a threshold value of 70 to 80 mm Hg. This low-volume strategy should be maintained until bleeding is controlled. Proponents of permissive hypotension suggest that administration of crystalloid may aggravate the inflammatory response, increase blood loss before definitive hemostasis, and increase transfusion requirements, which could further exacerbate early inflammation and late immunosuppression. Studies have examined the safety of permissive hypotension or restrictive resuscitation strategies in the prehospital, emergency department, and intraoperative phases of care. The landmark study by Bickell and colleagues[63] compared victims of penetrating torso trauma randomized to traditional fluid resuscitation or delayed resuscitation in the field and emergency department. The delayed group received no more than 100 mL of fluid before arrival in the operating room. Patients in the delayed group demonstrated a significant survival benefit (70% vs 62%), fewer complications, and a shorter hospital length of stay when compared with the traditional resuscitation group. Another prehospital study of patients with traumatic amputation found that restrictive prehospital fluid resuscitation strategies resulted in improved survival.[64] A study by Morrison and colleagues[65] compared low (50) versus traditional (65) mean arterial pressure goals to guide intraoperative resuscitation. The lower mean arterial pressure group experienced significantly less blood loss, had fewer transfusions, and had less crystalloid administered compared with the traditional group. The lower group had significantly improved early survival (98% vs 83%) and maintained a trend toward improved mortality at 30 days. As with the study by Bickell and colleagues,[63] the beneficial effects were most significant for victims of penetrating trauma. Unfortunately, few other studies have been able to replicate these positive effects, and active debate continues regarding the benefits of permissive hypotension. Its application, if used, should be limited to penetrating torso trauma victims.

Blood products

Evidence supporting early aggressive use of blood products for resuscitation came from work performed by the military. Austere combat settings limited access to large volumes of crystalloid and separated blood components; however, "walking blood banks" and fresh whole blood (FWB) were available. Studies of these patients revealed improved survival when FWB rather than PRBCs or traditional component therapy was used for resuscitation, and FWB was found to be associated with minimal infectious risk in these military populations.[18,66,67] Unlike the military, the civilian trauma patient is unlikely to have access to a reliable, homogenous, and immediately available "walking blood bank," and therefore, studies have focused on the effect of increasing the FFP-to-PRBC and platelets-to-PRBC ratios in an effort to mimic the composition of FWB for resuscitation of patients with MT. Two studies from the military revealed decreased mortality in a stepwise fashion with increasing plasma-to-PRBC ratios, with optimal results approaching a ratio of 1:1.[68–70] Civilian literature has also reflected improved mortality, with FFP-to-PRBC ratios approaching 1:1 (**Table 3**).[4,62,71–77] Unfortunately, most of these studies have been retrospective in nature and handicapped by the potential for survivor bias. A group in Germany has tried to compensate for this bias by performing a time-dependent covariate analysis among blunt trauma patients requiring MT, and found that even after correcting for survivor bias, an FFP-to-PRBC ratio of 1:1.5 or greater was associated with improved survival.[78] Studies of platelets-to-PRBC ratios have shown similar improvements in mortality, with higher ratios among patients undergoing MT (**Table 4**).[71,77,79–82] Lastly, studies of fibrinogen replacement have also supported both protocolized and TEG/ROTEM-guided supplementation of fibrinogen in the resuscitation of patients undergoing MT.[80,81,83–85] In contrast to FFP and platelets, which are available as single and pooled donor units only, fibrinogen can be supplemented using cryoprecipitate for transfusion or through administration of a concentrate derived from human plasma. Each vial contains between 900 and 1300 mg of lyophilized fibrinogen, which is reconstituted in as little as 50 mL of saline. Overall, a benefit does appear to be demonstrated from higher FFP-to-PRBC, platelets-to-PRBC, and fibrinogen-to-PRBC ratios during acute resuscitation of the MBL/MT patient. Although the ideal ratio

Table 3
FFP-to-PRBC ratio and outcomes

Study	FFP-to-PRBC Ratio	Outcome
Military		
Borgman et al,[70] 2007	1:1.4	Improved mortality
Van et al,[69] 2010	<1:4	Improved mortality, no change MSOF
Civilian		
Sperry et al,[73] 2008	≥1:1.5	Improved mortality, increased ARDS
Kashuk et al,[72] 2008	1:2–1:3	Improved mortality
Holcomb et al,[71] 2008	≥1:2	Improved mortality
Gunter et al,[77] 2008	≥2:3	Improved mortality
Teixeira et al,[74] 2009	>1:3	Improved mortality
Snyder et al,[76] 2009	>1:2	Improved mortality
Duchesne et al,[4] 2009	1:1 vs 1:4	Improved mortality
Lustenberger et al,[78] 2011	≥1:1.5	Improved mortality

Abbreviations: ARDS, acute respiratory distress syndrome; MSOF, multisystem organ failure.

Table 4
Platelets-to-PRBC ratio and outcomes

Study	Platelets-to-PRBC	Outcome
Military		
Perkins et al,[80] 2009	≥1:8	Improved mortality
Civilian		
Gunter et al,[77] 2008	≥1:5	Improved mortality
Holcomb et al,[71] 2008	≥1:2	Improved mortality
Zink et al,[82] 2009	≥1:4	Improved mortality
Inaba et al,[79] 2010	≥1:6	Improved mortality
Shaz et al,[81] 2010	≥1:2	Improved mortality

of each component is still unknown, 2 prospective trials are currently enrolling patients in an attempt to further delineate the ideal ratio of blood components for resuscitation and to answer definitively the question of survivor bias.[86,87]

Hemostatic adjuncts

In addition to a balanced transfusion strategy, several pharmacologic agents can be used as adjuncts to treat coagulopathy, including tranexamic acid, recombinant human factor VIIa, and prothrombin complex, which contains factors II, VII, IX, X, C, and S. Some evidence shows that use of these agents may decrease mortality, transfusion requirements, and rates of transfusion-related organ failure among certain trauma patients.

Factor VIIa

Initially developed for treatment of hemophilia, activated factor VIIa has been used to treat several trauma scenarios, including trauma-induced coagulopathy and reversal of anticoagulation in patients with brain injury. A randomized controlled trial of recombinant factor VIIa showed a decrease in PRBC transfusions and the percentage of patients requiring MT after blunt trauma.[88] A follow-up study from the same group confirmed the benefit of decreased transfusion requirements, and demonstrated lower rates of multisystem organ failure and ARDS associated with factor VIIa.[89] Although neither study found any increase in complications associated with factor VIIa, both studies were unable to confirm a mortality benefit. A study by Morse and colleagues[90] examining the protocolized use of factor VIIa as an adjunct in MT confirmed that it resulted in significantly decreased transfusion requirements, and also found a benefit in early mortality in the subset of patients receiving 30 units or greater of PRBCs (24-hour mortality, 26% vs 64%). Unfortunately, this benefit did not persist at 30 days. Subsequent studies, including a large multinational randomized controlled trial (CONTROL trial) also failed to confirm any significant mortality benefit in a variety of patient groups.[90–93] Additionally, concerns have been raised regarding increased thromboembolic complications, particularly those affecting the arterial circulation, associated with the use of factor VIIa.[92,94,95] Although factor VIIa is likely safe among patients with MBL, it is unlikely to be beneficial and therefore its use in DCR cannot be recommended.

Prothrombin complex

Prothrombin complex comes in a variety of formulations, all of which contain some combination of vitamin K–dependent coagulation factors. Three-factor prothrombin

complex formulations contain factor II, IX, and X. Four-factor prothrombin complex formulations contain factor II, VII, IX, and X. Both 3- and 4-factor formulations also contain variable amounts of protein C and S. Several studies have compared PCC with FFP and vitamin K for reversal of pharmacologic coagulopathy after injury or in anticipation of emergent surgery or invasive procedures. These studies uniformly found that prothrombin complex was faster and more efficacious than FFP and vitamin K at correcting international normalized ratio (INR) without any significant increase in complications.[96–100] Normalization of laboratory values of coagulation was achieved in as quickly as 30 minutes after administration of prothrombin complex, although in some instances reversal was not as durable as that achieved with vitamin K.[98,100] Recent studies examining prothrombin complex in trauma patients revealed trends toward improved mortality, decreased transfusion requirements, fewer complications, and shorter lengths of stay. In particular, the risk of multiorgan failure and need for mechanical ventilation were diminished with the use of prothrombin complex.[84,85,101–103] Concern exists over the potential for prothrombin complex to increase the risks of thromboembolic complications similar to factor VIIa. A recent meta-analysis of the studies of prothrombin complex to date found a rate of thromboembolic events of 1.4%.[104] However, no statistically significant increases in thrombotic events over controls have been noted in studies of trauma patients to date.[102,103,105]

Tranexamic acid

Tranexamic acid is a synthetic derivative of lysine. Tranexamic acid inhibits plasminogen activation and plasmin activity through bonding to the lysine binding site, blocking binding to fibrin. Unlike factor VIIa and prothrombin complex, its effects occur primarily through preventing fibrinolysis rather than promoting coagulation.[106] Two large prospective trials, one among civilian trauma patients and one among more severely injured military trauma victims, both found significant benefit from use of tranexamic acid. The CRASH-2 trial was a prospective randomized controlled trial of 20,211 trauma patients randomized to tranexamic acid infusion or placebo. Tranexamic acid was associated with an absolute decrease in all-cause mortality (14.5% vs 16%), with an RR of 0.91 (CI, 0.85–0.97; $P = .0035$). Mortality from bleeding was also decreased (4.9% vs 5.7%), with an RR of 0.85 (CI, 0.76–0.96; $P = .0077$). No statistically significant increases in either venous or arterial thromboembolic complications were noted. However, benefit was only found if tranexamic acid was given within 3 hours of injury; administration after 3 hours was associated with increased mortality.[107] The Military Application of Tranexamic Acid in Traumatic Emergency and Resuscitative Surgery (MATTERs) study examined a group of severely injured military trauma patients, of which 26% required MT. Tranexamic acid was administered within 1 hour of injury to 293 patients. Despite a higher injury severity, patients who received tranexamic acid had a significantly decreased unadjusted mortality (17.4% vs 23.9%). This benefit was even more pronounced among patients who received MT, with mortality decreased 13.7% (14.4% vs 28.1%). After multivariate logistic regression analysis, tranexamic acid was found to be an independent predictor of survival. Although an increase in venous thromboembolic complications was associated with tranexamic acid, it was not an independent predictor of thromboembolic complications in either the group as a whole or among patients who received MT.[108]

Massive transfusion protocols

Standardizing transfusion ratios with institutional massive transfusion protocols (MTP) has increased in popularity. The goal of an MTP is to standardize the replacement of platelets and clotting factors in an optimum ratio to PRBCs, and increase speed and

efficiency of transfusion. An MTP may include protocolized use of hemostatic adjuncts, such as tranexamic acid, prothrombin complex, and factor VIIa.

Carefully selected triggers of MTPs are important for 2 key reasons. First, rapid identification of patients likely to require MT and early aggressive transfusion of blood, FFP, and platelets has been associated with improved mortality.[109–111] Second, aggressive resuscitation and administration of higher ratios of FFP and platelets, when given to patients who are not massively bleeding, causes an unnecessary expenditure of resources and may result in worse outcomes for patients.[112–115] Indications for MTP include transfusion and clinical triggers. Transfusion triggers generally range between 6 and 10 units of PRBCs as a threshold to initiate MTP. Transfusion triggers are easily defined and adhered to, but may lead to delays in administration of FFP/platelets, because significant blood loss must have occurred before protocol initiation. Clinical variables commonly associated with MT include multicavitary trauma, penetrating mechanism, systolic blood pressure less than 90 mm Hg, heart rate greater than 120, anemia (hemoglobin <10) or coagulopathy (INR >1.5) at admission, and free fluid on focused assessment with sonography for trauma (FAST).[9,13,116,117] Clinical triggers are likely to result in earlier initiation of MTPs but use of any single element may be inaccurate. Therefore, several scoring systems have been created using multiple elements, including the trauma-associated severe hemorrhage (TASH) score, the McLaughlin score, and the assessment of blood consumption (ABC) score.[13,14,117] The TASH and McLaughlin scores include laboratory data such as hematocrit, pH, and base deficit, whereas the ABC score uses only clinical data immediately available on admission, which may make it a more useful tool. The ABC score consists of 4 elements: penetrating mechanism, positive FAST, blood pressure less than 90 mm Hg, and heart rate 120 or greater (**Table 5**). A score of 2 or more predicts MT with a sensitivity of 75% to 90% and specificity of 67% to 88% in initial studies.[9,13] When compared with the more complex TASH and McLaughlin scores, the ABC score was as or more accurate in predicting which patients would require MT.[12,13]

Initiation of an MTP is meant to increase communication among the surgeon/anesthesia team, laboratory, and blood bank, and increase ease and efficiency in ordering blood products. A growing body of evidence supports the efficacy of MTPs in the civilian trauma population. First and foremost, MTPs seem to be effective in achieving their primary goal of high FFP- and platelets-to-PRBC ratios, and significantly decreased crystalloid infusion.[10,118–120] Use of MTPs seems to decrease overall blood product use.[11,121] This finding may be because of prevention or more rapid treatment of coagulopathy, resulting in decreased total blood losses. Several studies show that the initiation of an MTP significantly decreases the time from admission to first transfusion, and the turnaround time for subsequent transfusions.[118,122] Meeting these goals of DCR decreases mortality and the percentage of patients developing acoagulopathy.[11,111,118–121] Although randomized controlled trials are lacking, multivariate analysis identifies DCR and MTP initiation as independent predictors of survival.[11,111,120,121] Additionally, a study performed solely after initiation of an institutional MTP found that compliance with all measures of the protocol improved survival (86.7% vs 45%; $P<.001$), and multivariate analysis identified compliance with MTP as an independent predictor of survival.[121] Efficacy in achieving high FFP-to-PRBC ratios and high survival rates is found with the use of MTPs among military personnel.[123] Analysis of survivors of MTP shows that decrease in mortality does not come at the cost of increased morbidity. Use of MTPs seems to result in significantly lower rates of ACS; decreased need for open abdomens; decreased rates of sepsis, particularly pneumonia; decreased rates of multiorgan failure, particularly respiratory failure;

Table 5
MTP predictive models

Scoring System	ABC	TASH[117]	McLaughlin[14]
Variables	ED SBP ≤90 mm Hg (1 pnt) ED HR ≥120 BPM (1 pnt) Penetrating trauma (1 pnt) +FAST (1 pnt)	SBP <100 mm Hg (4 pnts) SBP <120 mm Hg (1 pnt) HR >120 BPM (2 pnts) Hgb <7 (8 pnts) Hgb <9 (6 pnts) Hgb <10 (4 pnts) Hgb <11 (3 pnts) +FAST (3 pnts) Complex fracture AIS 3–4 (3 pnts) AIS 5 (6 pnts) BE <–10 (4 pnts) BE <–6 (3 pnts) BE <–2 (1 pnt) Gender (male = 1 pnt)	SBP <110 mm Hg HR >105 BPM pH <7.25 Hct <32%
Predictive value	Score 2 = 38% MTP Score 3 = 45% MTP Score 4 = 100% MTP	Score ≥16 = 50% MTP Score ≥27 = 100% MTP	Score 1 = 20% MTP Score 4 = 80% MTP
Comparative accuracy Nunez et al,[13] 2009 Krumrei et al,[12] 2012	AROC = 0.842 AROC = 0.86	AROC = 0.842 AROC = 0.51	AROC = 0.846 AROC = 0.56

Abbreviations: AIS, abbreviated injury score; AROC, area under the receiver operating characteristic; BE, base excess; BPM, beats per minute; ED, emergency department; Hct, hematocrit; Hgb, hemoglobin; HR, heart rate; pnt, point; SBP, systolic blood pressure.

and decreased hospital length of stay. Lastly, some evidence shows that MTPs may significantly decrease hospital costs.[122]

Role of Laboratory Guidance

Classical measures of coagulopathy, such as PT/INR and aPTT, which are warmed to standard body temperature (37°C) before analysis, may falsely normalize results and lead to underdiagnosis of coagulopathy. These tests do not address platelet dysfunction caused by medications, hypothermia, or fibrinolysis, further underestimating coagulopathy. In fact, several studies that reported clinically evident coagulopathy found that these traditional laboratory values correlate poorly with clinical evidence of medical bleeding in humans and animals.[19,124] Additionally PT, aPTT, and complete blood cell counts often require 30 minutes to more than an hour before results are available, potentially delaying treatment of trauma-related coagulopathy.[57,125] These limitations of traditional measures of coagulopathy have led to a resurgence in the use of alternative measures of clotting and clot strength, including TEG or ROTEM. TEG and ROTEM work similarly and measure the viscoelastic properties of a patient's blood sample. TEG/ROTEM have the benefit of rapidly providing detailed information on clot formation and strength, and are run at patient temperatures, potentially improving accuracy in diagnosing coagulopathy. In the resuscitation of trauma patients in severe hemorrhagic shock, TEG/ROTEM can have 2 potential applications: results drawn at admission can be used to predict and trigger MTPs, and serial results can be used to direct ongoing blood component therapy. Persuasive evidence

currently shows that TEG/ROTEM are beneficial in both roles. Several studies have proven TEG/ROTEM to be good predictors of the need for transfusion and MT, and of mortality.[10,56,125–128] Additionally, several of these studies compared TEG/ROTEM results with standard laboratory findings (PT/INR and aPTT) and found them to have a higher sensitivity for detecting coagulopathy on admission and an improved accuracy in predicting transfusion, MT, and mortality.[10,56,125,128]

TEG/ROTEM results are available to the clinician running the resuscitation significantly quicker than traditional laboratory measures of coagulopathy, with initial results available within 5 minutes.[10,125] When used in ongoing resuscitation or as part of an MTP, TEG/ROTEM was associated with shorter time to first transfusion, higher FFP-to-PRBC ratios, and increased platelet transfusion.[52,129] Effect of TEG/ROTEM use on mortality is unclear, but some evidence suggests a survival benefit. In a study of trauma patients, ROTEM-guided resuscitation resulted in mortality significantly less than that predicted by the trauma score–injury severity score, or TRISS (24.4% vs 33.7%; $P = .032$). This survival benefit was even more dramatic after excluding patients with isolated TBI (14% vs 27.8%; $P = .0018$).[84] Another study of patients requiring MT treated before and after initiation of MTP with TEG found that MTP with TEG guidance was associated with a significant improvement in 30-day (20.4% vs 31.5%; $P = .0002$) and 90-day mortality (22.4% vs 34.6%; $P<.0001$).[129]

Efficacy

Damage control resuscitation, including permissive hypotension, early use of blood products, more aggressive coagulation factor replacement, and MTPs, seems to have had a beneficial effect on outcomes. A study reviewing patients with MBL who were resuscitated with classical techniques within the period of 1970 to 1990 showed that they experienced very poor outcomes, with mortality ranging from 61% to 90%.[7,19,60,61,130] These findings improved somewhat in later studies conducted from 1990 to the 2000s, but survival was still poor, ranging from 45% to 87%.[3,4,111,118,119,130] In contrast, current mortality rates after initiation of DCR and MTPs range from 8% to 34%.[3,4,54,55,111,118,123]

VASOACTIVE AGENTS

Because of the morbidity associated with excessive fluid administration and the paucity of evidence supporting permissive hypotension outside of penetrating trauma, many investigators have begun examining the role of early vasopressor use in patients with hypovolemic shock. Early use of vasopressors, particularly before definitive hemostasis, has the theoretical benefit of allowing the surgeon to maintain an acceptable mean arterial pressure while avoiding the need for large volume fluid administration. Several animal models show that endogenous vasopressin is required to maintain blood pressure in response to hemorrhage, and exogenous vasopressin can act as an effective vasopressor, reversing advanced hemorrhagic shock more effectively than other agents or fluid administration.[131–134] Vasopressin use resulted in significantly decreased blood loss and improved survival in several of these studies.[131,134] Data suggest a deficit of endogenous vasopressin after hemorrhagic shock in association with TBI.[135,136] Human data supporting the use of vasopressin in the acute resuscitation period are lacking. A single prospective randomized controlled trial of patients who experienced hypotensive trauma randomized to standard fluid resuscitation or resuscitation with bolus then infusion of vasopressin after trauma found a nonsignificant improvement in mortality (13% vs 25%; $P = .19$). This study also found that the vasopressin group received significantly less fluid in

the first 5 days; however, this did not translate into any benefit in terms of 30-day mortality, morbidity, or organ dysfunction.[137] Another small study of patients experiencing blunt traumatic arrest found that the addition of vasopressin and hydroxyethyl starch to standard cardiopulmonary resuscitation resulted in increased return of spontaneous circulation and 24-hour survival.[138] However, 3 large retrospective studies of severely injured and hypotensive trauma patients found the administration of vasopressin was associated with significantly increased risk of death regardless of volume status.[139–141] Evidence is currently insufficient to recommend the use of vasopressin or other vasoactive agents as a substitute for aggressive fluid resuscitation in the acute period after trauma.

SUMMARY

Patients with MBL resulting in hemorrhagic shock requiring an MT account for a small percentage of total trauma admissions. However, they account for a significant percentage of potentially preventable deaths. DCR techniques, including selective use of permissive hypotension, avoidance of overly aggressive crystalloid resuscitation, and early aggressive transfusion strategies with higher FFP-to-platelets-to-PRBC ratios have improved mortality over previous decades. MTPs are useful institutional tools for improving communication between the blood bank and the clinician. MTPs improve availability of blood products, decrease times to transfusion, likely improve mortality, and may decrease cost. Tranexamic acid and prothrombin complex may be beneficial adjuncts to resuscitation of patients in hemorrhagic shock. Viscoelastic testing using TEG/ROTEM is useful in predicting and triggering MTPs and in guiding ongoing resuscitation.

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