Resuscitation

5

Phillip Kemp Bohan and Martin A. Schreiber

Introduction

Explosive blasts can produce highly variable patterns of injury. Rapidly changing pressures between tissues of different densities lead to primary injury, while damage from projectiles and surrounding structures in the proximity of the blast results in secondary and tertiary injury, respectively (see Fig. 5.1). Primary injury has been shown to affect the tympanic membranes, lungs, and hollow viscera more frequently than other organ systems; however, injuries produced through secondary and tertiary injury are dependent on a number of different variables and can be extremely unpredictable [1]. Blast injury, most commonly from improvised explosive devices (IEDs), has been the primary mechanism of injury in the wars in Iraq and Afghanistan, though recent attacks on civilian populations have also forced civilian trauma centers to resuscitate and manage blast-injured patients (see Fig. 5.2).

Resuscitation of blast-injured patients draws upon the broader principles of resuscitation in trauma but also requires an individualized approach to each patient to ensure that each type of injury is appropriately addressed. Patients noted to have shattered tympanic membranes on initial survey may also harbor profound occult lung injury from blast-associated barotrauma. Following the tympanic membrane, the lung is the most commonly injured organ in blast-associated trauma. Excessive fluid administration during resuscitation in these patients would exacerbate any underlying lung trauma and potentially result in severe respiratory distress. However, patients with extensive secondary and tertiary injuries who present with signs of hemorrhagic shock will require immediate and focused resuscitative efforts.

The broad goals of resuscitation are to restore adequate intravascular volume, augment the body's natural clotting ability, slow or prevent the development of coagulopathy, and maintain end-organ perfusion [2]. This chapter will discuss methods of resuscitation, current practice guidelines, and suggestions for the amendment of these guidelines based on specifics of the blast-injured patient and blast scenarios. Particular attention will be given to early high-ratio blood component therapy, the reemergence of whole blood resuscitation, and specific considerations for resuscitation in blast-injured patients. A significant amount of relatively new data concerning resuscitation in trauma comes from the wars in Iraq and Afghanistan. As blast injury was most common in those populations, this data applies directly to the topic of this chapter.

P. Kemp Bohan (✉)
San Antonio Military Medical Center,
Ft. Sam Houston, TX, USA

M. A. Schreiber
Division of Trauma, Critical Care, and Acute Care Surgery, Oregon Health & Science University,
Portland, OR, USA

J. M. Galante et al. (eds.), *Managing Dismounted Complex Blast Injuries in Military & Civilian Settings*, https://doi.org/10.1007/978-3-319-74672-2_5

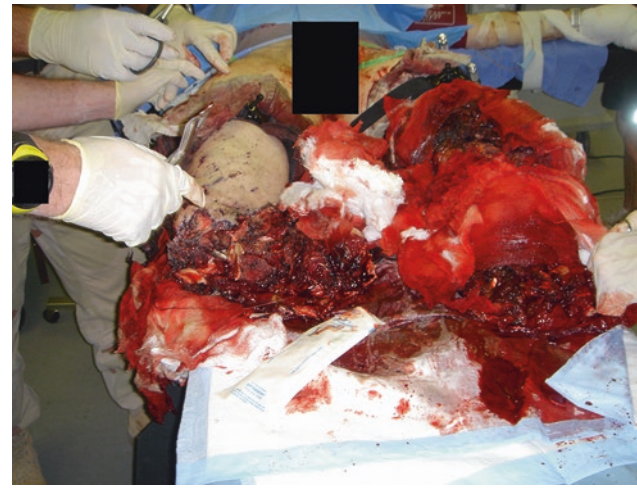

Fig. 5.1 A combat casualty with traumatic amputation of both lower extremities secondary to blast injury. Tourniquets were placed proximally for hemorrhage control in the field

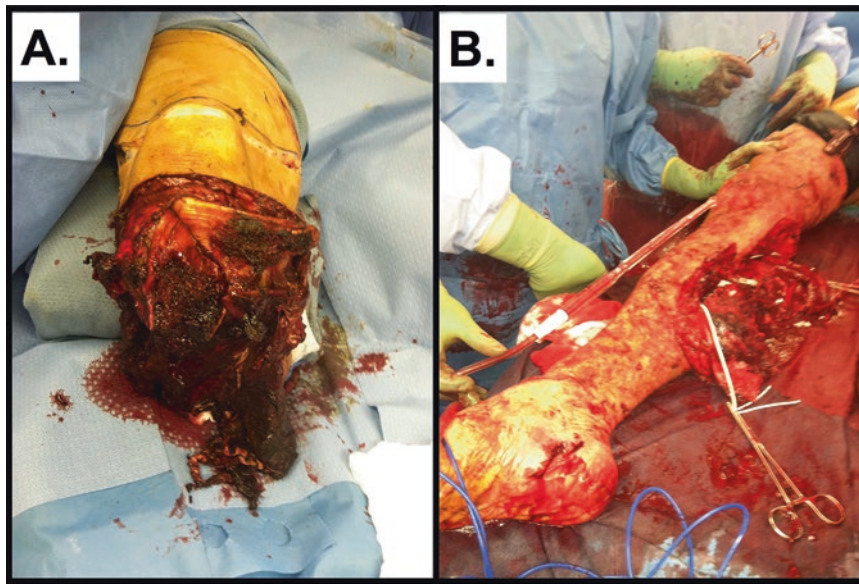

Fig. 5.2 Injuries seen after the 2013 Boston Marathon bombing including major extremity amputations (panel A) and mangled extremity injuries with significant bony and soft tissue damage (panel B) (Photos courtesy of Dr. George Velmahos)

Methods of Resuscitation

Resuscitation Fluids: Crystalloid and Colloid

Resuscitation fluids can broadly be categorized as either crystalloids or colloids. Crystalloid solutions contain varying concentrations of ions and are categorized as hypo-, iso-, or hypertonic, depending on the relative concentrations of the solution and blood. Examples of crystalloid solutions include normal saline (NS) and lactated Ringer's (LR) solution. Colloids contain large osmotic molecules designed to remain in the intravascular space. These molecules increase the osmotic pressure of the intravascular space, drawing in and theoretically holding fluid in that space

Table 5.1 Commonly available resuscitation fluids

Generic formulation	Trade name
Crystalloids	
0.9% saline	Normal saline (NS)
Compounded sodium lactate	Lactated Ringer's (LR)
Balanced crystalloid solution	PlasmaLyte
Colloids	
4% human albumin	Albumex 4
6% hetastarch in lactated electrolyte solution	Hextend
6% hetastarch in 0.9% saline	Hespan
6% hydroxyethyl starch in 0.9% saline	Voluven
4% succinylated gelatin in 0.7% saline	Gelofusine
Low molecular weight dextran in 5% dextrose	Dextran-40

Commonly encountered resuscitation fluids, divided into crystalloids and colloids. Normal saline is considered the reference crystalloid fluid, while 4% albumin is the reference colloid

to buttress intravascular volume. Examples of colloid solutions include hydroxyethyl starches, gelatins, and dextrans (see Table 5.1) [3].

Large-volume resuscitation with crystalloid for hemorrhaging patients rose to prominence in the Vietnam War and continued throughout the remainder of the twentieth century, despite reports of decreased mortality utilizing delayed resuscitation or plasma/blood product resuscitation [4]. The rise in crystalloid resuscitation corresponded with the development of technology capable of separating whole blood into components. Blood products could now be stored for longer periods of time, but emergency resuscitation with blood products became much more difficult as each product required significant preparation prior to transfusion. Crystalloid offered a quicker, cheaper means of rapidly supporting depleted intravascular volume and restoring perfusion pressure in hemorrhaging patients [5]. In addition, the logistical requirements for shipping, storing, and carrying crystalloids are much lower compared to blood products, which made them particularly attractive for application in resource-constrained settings such as the battlefield.

When comparing crystalloid to colloid as a primary resuscitative fluid, there is no appreciable difference in survival rate [6, 7]. The utilization of one fluid or the other is driven by cost and practicality. Compared to colloid, crystalloid is less expensive per unit but requires a larger transfusion volume to produce a significant change in intravascular volume status. In the civilian setting, where EMS providers are able to carry liters of NS or LR at all times, crystalloid is typically the resuscitative fluid of choice because it is cheaper. However, in the military, in austere and far-forward settings, colloids are preferred due to weight and volume considerations.

Despite the initial support for crystalloid and colloid as intravascular volume expanders, both types of resuscitative fluids are associated with a number of significant complications. First, and perhaps most importantly, rapidly restoring perfusion pressure prior to the definitive surgical control of bleeding increases the likelihood of "popping the clot" and rebleeding from the initial wound. First described in 1918 by Dr. W. B. Cannon [8], a US Army surgeon in World War I, rebleeding secondary to resuscitation only gained traction in the trauma community in the early 1990s. In 1991, Bickell et al. compared resuscitation with 80 ml/kg LR to no resuscitation in a swine hemorrhage model and found that both hemorrhage volume and mortality rate were significantly higher in the group receiving LR when compared to the untreated group [9]. Building on this data, Bickell et al. then conducted a prospective trial in 1994 that compared immediate resuscitation to delayed resuscitation following surgical control of hemorrhage in penetrating torso trauma patients who presented with a systolic BP $\leq$90 mmHg. The group found that survival was higher in patients receiving delayed resuscitation compared to immediate resuscitation (70% vs 62%, $p = 0.04$) [4]. This landmark study definitively demonstrated the dangers of rebleeding following resuscitation.

A second problem with crystalloid resuscitation is that while the initial bolus of volume creates enough pressure to dislodge a nascent clot, only a small fraction of the infusion actually remains within the vasculature in the ensuing minutes and hours. Up to 90% of isotonic crystalloid is ultimately "third-spaced" to extravascular

interstitial spaces, resulting in tissue swelling and further organ injury [10]. This phenomenon may be exacerbated by diffuse tissue injury produced by blast injury. The important association between massive fluid resuscitation and lung injury was described first during the Vietnam War, where soldiers with no evidence of lung injury developed acute respiratory distress syndrome following aggressive crystalloid resuscitation [11]. Additional studies have noted crystalloid resuscitation to be a risk factor for abdominal compartment syndrome in trauma patients with no abdominal injury (secondary abdominal compartment syndrome) [12, 13]. Specifically in blast-injured patients, third-spacing of fluid can easily exacerbate underlying lung injury from primary blast trauma and result in rapid respiratory compromise.

Finally, large-volume crystalloid administration causes hemodilution and can exacerbate acute traumatic coagulopathy (ATC). Recent literature has demonstrated that hemodilution and ATC should be approached as two distinct entities. Hemodilution occurs with the administration of massive crystalloid volumes without compensatory supplementation of platelets, red blood cells, and clotting factors. Separately, ATC is a protein-C-mediated hypocoagulable state that can develop in severely injured patients [14–16]. While the two processes are distinct, they can be difficult to examine independently as hemodilution likely exacerbates ATC [14]. The study by Bickell et al. revealed that hemoglobin and platelet levels were significantly lower and prothrombin time (PT) and partial thromboplastin time (PTT) were significantly longer in the immediate-resuscitation group when compared to the delayed-resuscitation group at admission; [4] each of these laboratory findings points to the presence of a coagulopathy. The study was not designed to elucidate the relative contributions of hemodilution and ATC to the development of coagulopathy, though it is likely that a combination of both processes resulted in the development of a hypocoagulable state. A final important point is the rapidity with which the coagulopathy developed: coagulopathy was present in these patients as they arrived, prior to any intervention [4].

Hypotensive Resuscitation

While Bickell et al. proposed the theory of rebleeding as a result of resuscitation in their landmark study [4], no controlled experiments had been performed to formally investigate this hypothesis until Sondeen et al. [17] explored the question using a swine hemorrhage model in 2003. The group found that in pigs subjected to massive hemorrhage and then resuscitated with LR, rebleeding occurred once the systolic BP reached 94 ± 3 mmHg. The authors studied the effects of multiple injury sizes (1.5, 2.0, and 2.8 mm punch aortotomies) with the hypothesis that injury size would play a role in rebleeding. Interestingly, while larger injuries resulted in larger volumes of initial blood loss, the authors found no relationship between injury size and rebleeding systolic blood pressure. This finding further strengthened the conclusion that the propensity of a vessel to rebleed is driven predominantly by the blood pressure [17].

Hypotensive resuscitation, also known as permissive hypotension, is the judicious administration of fluids to an actively bleeding patient in order to achieve the goals of resuscitation while avoiding complications associated with rebleeding. Importantly, permissive hypotension should not be interpreted as providing absolutely no fluid resuscitation to the patient prior to gaining surgical control of bleeding. Capone et al. showed that rats resuscitated to a mean arterial pressure of 40 mmHg prior to surgical control of bleeding had similar 2.5-h mortality but improved 3-day survival when compared to rats not resuscitated with any fluid prior to surgery [18]. More recently, Hampton et al. compared outcomes among 1200 level 1 trauma patients who either received no prehospital fluids (n = 191) or any prehospital fluids (n = 1009) [19]. The authors found that prehospital fluid administration was associated with decreased in-hospital mortality (hazard ratio [HR] 0.84; 95% CI 0.72–0.98) [19].

These studies should not be viewed as antagonistic to the findings of Bickell et al. [4] Just as excessive fluid administration can lead to immediate rebleeding problems in severely injured trauma patients, no fluid administration at the

time of initial injury results in a deficiency in end-organ perfusion that only manifests in the days following injury. Hypotensive resuscitation seeks to balance these two competing sets of complications by initially restoring a low but adequate perfusion pressure through fluid administration in the field and maintaining this until surgical control of bleeding can be achieved, at which time more aggressive measures to restore volume and mitigate the effects of tissue hypoperfusion can be attempted.

Damage Control Resuscitation

Damage control resuscitation (DCR) is the combination of permissive hypotension with early initiation of high-ratio blood component therapy, minimization of crystalloid usage, and rapid and definitive hemorrhage control [20]. A driving force behind the development of DCR was an improved understanding of coagulopathy in trauma patients and the recognition that hypotensive resuscitation alone did not address this coagulopathy. Early coagulopathy develops in 20–30% of severely injured trauma patients and is a harbinger of future morbidity and mortality [21, 22]. In a retrospective review of 7638 trauma patients, MacLeod et al. showed that mortality was 3.6 times more likely in patients with an abnormal PT (95% CI 3.15–4.08) and 7.81 times more likely in patients with an abnormal PTT (95% CI 6.65–9.17) on admission [21]. Similarly, Brohi et al. reviewed 1867 trauma patients and found that patients who were coagulopathic on presentation had a higher mortality (46.0% vs 10.6%, $p < 0.001$) [22]. Importantly, the authors also noted that the development of coagulopathy was unrelated to the volume of crystalloid or colloid given to a patient [22]. These patients developed coagulopathy despite limited fluid resuscitation, suggesting that hypotensive resuscitation alone was insufficient at combating ATC.

Of the four tenants of DCR, the most controversial over the past decade has been that of high-ratio resuscitation. The benefits of high-ratio resuscitation were noted first during the recent wars in Afghanistan and Iraq. Borgman et al. reviewed 246 US Army casualties, the majority of whom had suffered blast mechanism injuries, and found that rates of overall morbidity and mortality secondary to hemorrhage were significantly higher in patients resuscitated with lower ratios (1:8) of plasma and RBCs when compared to patients resuscitated with higher ratios (1:1.4) of plasma and RBCs [23]. While later retrospective studies supported this initial finding [24, 25], a weakness of these studies was the potential for survival bias: patients who lived longer received higher ratios of products, while patients who died early did so before plasma and platelets could be administered (see Fig. 5.3).

Holcomb et al. conducted the Pragmatic Randomized Optimal Platelet and Plasma Ratios (PROPPR) trial in 2015. The study was a randomized controlled trial comparing blood product ratios of 1:1:1 and 1:1:2 (plasma, platelets, and PRBCs) during initial resuscitation [26]. This prospective and randomized study design minimized the likelihood that survival bias would

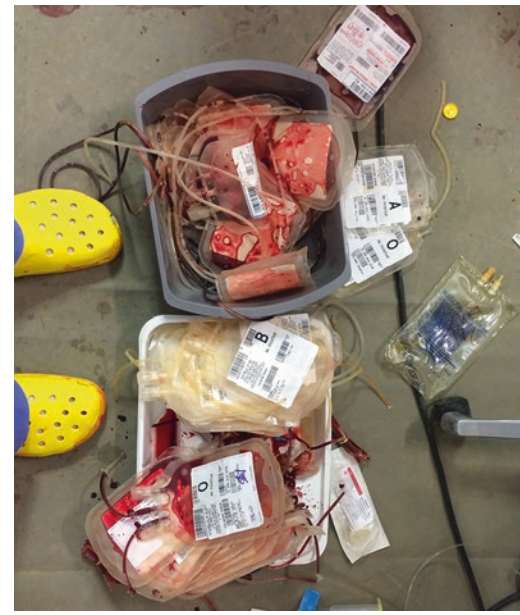

Fig. 5.3 Balanced resuscitation in theater. Early in the conflict, 1:1:1 resuscitation was found to be superior to low-ratio resuscitation. However, given the limitations of the retrospective studies and concern for survivor bias in the early literature, it was not until Holcomb et al. published the results of the PROPPR study that 1:1:1 became accepted in civilian practice

significantly impact the study results. The authors found that while there was no overall mortality benefit associated with high-ratio resuscitation, patients who received a 1:1:1 ratio of plasma, platelets, and PRBCs achieved hemostasis more frequently and had fewer early deaths due to exsanguination than patients receiving 1:1:2 ratio resuscitation [26]. Further, the authors noted that the median time to death from hemorrhage was 2.3 h [26]. Following PROPPR, 1:1:1 has become standard empiric therapy for early resuscitative efforts in most US trauma centers, although there remains a significant debate about the optimal ratio of blood products for damage control resuscitation. What has become generally agreed upon is that an early balanced resuscitation focusing on both restoring circulating red blood cell mass and providing clotting factors and platelets is clearly superior to the previous strategy of administering larger volumes of crystalloids and then packed red blood cells and delaying initiation of plasma or platelet transfusion until much later in the resuscitation.

While high-ratio resuscitation is the driving component of DCR, the same principles of minimizing supplementary fluid administration and permissive hypotension prior to definitive control of bleeding are still critical. In a retrospective analysis of 307 trauma patients with severe hemorrhage managed with high-ratio DCR, Duke et al. found that patients who received <150 mL crystalloid in the ED had lower intraoperative mortality and improved survival when compared to patients who received ≥150 mL crystalloid during the initial ED resuscitation [27]. Similarly, in a separate study, Guidry et al. evaluated fluid administration in trauma patients who received ≥4 units PRBCs and high-ratio resuscitation and found that higher volumes of crystalloid administration in the setting of DCR was associated with overall decreased survival [28]. Finally, Schreiber et al. randomized 192 trauma patients with an SBP <70 mmHg or with no palpable radial pulse in the field to receive either controlled resuscitation (250 mL initially and then 250 mL boluses for loss of radial pulse or SBP <70 mmHg) or standard resuscitation (2 L initially and then fluid as needed to maintain an SBP of 110 mmHg or greater) [29]. The authors noted that among blunt trauma patients, 24-h mortality was 3% in the controlled resuscitation group and 18% in the standard resuscitation group (OR 0.17, 95%CI 0.03–0.92) [29]. Taken together, these data suggest that while each component of DCR conveys a certain survival benefit alone, the ability to unite these various components into a single resuscitation paradigm predictably provides the greatest benefit to the patient.

The greatest limitation of component therapy lies in the process of separating and storing the components. In theory, resuscitation using a 1:1:1 ratio of components should roughly approximate resuscitation with whole blood. However, the separation of a unit of whole blood into components and the storage solutions used to preserve component longevity both result in a significant dilution of RBCs, platelets, and clotting factors. Up to 40% of coagulation factors from the whole blood unit are lost in the process; similarly, significant decreases in both platelet function and platelet number also occur [30]. When components are given back in a 1:1:1 ratio, the patient receives a much less potent version of reconstituted whole blood that produces a dilutional effect and provides only a fraction of whole blood functionality.

An additional consideration when transfusing blood products is the age of the products themselves. In non-leukoreduced, non-washed blood, breakdown products and cytotoxic elements accumulate over time and create a solution capable of producing a pro-inflammatory state in the recipient's endothelium [31]. Lipids and plasma isolated from non-leukoreduced stored blood have been shown to induce significant tissue injury in in vivo models [32]. Zallen et al. examined the relationship of age of blood to multiorgan failure by retrospectively comparing trauma patients who received between 6 and 20 units of RBCs in the first 12 h after injury. The authors found that patients who developed multiorgan failure received significantly older RBC units and that the age of RBC units was an independent predictor for multiorgan failure [33]. Thus, component therapy is limited not only by a dilution of product but by the degeneration of the product

and the accumulation of pro-inflammatory markers that can exacerbate the inflammatory response already present in trauma patients.

Whole Blood Resuscitation

From World War I through the Vietnam War, transfusion with whole blood was the preferred means of resuscitation for massively hemorrhaging soldiers. Component therapy replaced whole blood transfusion following the Vietnam War not because component therapy was demonstrated to have improved outcomes but because of technologic advances that allowed for the separation and long-term storage of components [34]. Whole blood comes in two varieties: warm, fresh, whole blood (WFWB) and stored whole blood (SWB). WFWB is transfused within 24 h of the time of collection, while stored whole blood is mixed with a citrate-containing solution to prevent clot formation and then refrigerated for up to 21 days [34]. In combat environments, WFWB is the more likely source of whole blood and is drawn from a "walking blood bank" of soldiers previously screened for blood-borne disease and blood-typed to identify ABO antigens.

The recent wars in Iraq and Afghanistan have led to a resurgence in the use of whole blood as a viable method of resuscitation. Given the difficulties in maintaining a blood supply network in combat theaters, especially during the more kinetic phases of the wars, both forward surgical teams and combat support hospitals (CSHs) had limited access to platelets and plasma [35]. Further, the arrival of even one or two casualties requiring massive transfusion (>10 units PRBCs in 24 h) in quick succession could rapidly deplete the component reserve [36]. When blood components were unavailable or when demand was predicted to far outstrip the blood bank's supply of component therapy, whole blood became a reliable and necessary adjunctive therapy. One US CSH in Iraq described a massive transfusion protocol in which blood drive efforts began immediately upon the identification of a casualty requiring massive transfusion [36]. Casualties received a single massive transfusion pack (4 units PRBCs, 4 units FFP, 10 units cryoprecipitate) during the initial resuscitative effort but were transitioned to whole blood transfusion within an hour of arrival [36].

There are few randomized controlled trials that compare the outcomes of whole blood versus blood component resuscitation. In 1991, Manno et al. assessed whether WFWB was associated with improved hemostasis after cardiopulmonary bypass in children [37]. The authors randomly assigned children to receive WFWB (Group I), whole blood administered 24–48 h after donation (Group II), or RBC, FFP, and platelets (Group III, component therapy) and measured 24-h blood loss to assess the degree of hemostasis. Blood was stored either at room temperature (Group I, WFWB) or 4–6 °C (Group II, delayed transfusion). There was no significant difference between groups in the volume of blood transfused. However, mean 24-h blood loss was much lower in the groups receiving whole blood (50.9 mL/kg in Group I, 44.8 mL/kg in Group II) than component therapy (74.2 mL/kg in Group III; $p = 0.03$). The generalizability of this study to the trauma population is questionable, though this early data does suggest a benefit for patients receiving young whole blood transfusion [37].

In 2013, Cotton et al. conducted the first randomized controlled trial in the trauma setting that compared whole blood and component resuscitation [38]. Trauma patients with obvious active bleeding who required emergent uncrossmatched blood on ED arrival were randomized to receive leukoreduced whole blood stored at 1–6 °C for up to 5 days or component therapy (RBCs, plasma, and platelets). As the process of leukoreduction of whole blood results in the removal of platelets, whole blood transfusions were supplemented with apheresis platelets (modified whole blood, or mWB). The primary outcome was total blood product use in the first 24 h. The authors found no differences in the 24-h RBC, plasma, or platelet use between the two study groups, nor were there differences in the median blood volume transfused in the first 24 h. However, a significantly larger percentage of patients with traumatic brain injuries (TBIs) were enrolled in the mWB group; after excluding all patients with TBI and repeating

the analysis, the authors found that the 24-h RBC, plasma, platelet, and total product use were all significantly lower in the group receiving mWB. There was no difference in 24-h or 30-day mortality between the two groups in either the overall or subgroup analysis. The authors concluded that in patients without severe TBI, mWB reduced overall transfusion volume when compared to component therapy [38].

A number of retrospective (and thus inherently limited) studies have demonstrated improved survival when comparing patients receiving WFWB to those receiving components. Nessen et al. examined survival in combat casualties who received RBCs, FFP, and WFWB to those who only received RBC and FFP and found that the addition of WFWB appeared to result in improved in-hospital survival [39]. Spinella et al. compared casualties receiving RBCs, plasma, and WFWB to those who received RBCs, plasma, and platelets and found that both 24-h and 30-day survival rates were higher in the WFWB cohort [40]. Blast injury was the most common mechanism of injury in these studies. While these data suggest WFWB is associated with a survival benefit, more rigorous clinical trials are needed to definitively demonstrate this.

The two obvious concerns when using whole blood for resuscitation are the development of an acute transfusion reaction and the transmission of blood-borne pathogens, notably hepatitis B, hepatitis C, and HIV. Transfusion reactions can occur either through host antibodies attacking donor cells or donor antibodies attacking host cells. Historically, group O blood has been considered universally compatible blood because group O RBCs should express no A or B antibodies. However, group O donor plasma can still contain anti-A or anti-B IgG that can produce a hemolytic reaction [41]. The concentrations of anti-A or anti-B can be quantified and loosely grouped into "high-titer" and "low-titer" plasma; low-titer anti-A/anti-B whole blood is considered safer as it carries a lower risk of transfusion reactions [41, 42]. A study reviewing adverse events in the UK blood services found that the rate of total adverse reactions for transfusion of any blood product is 10 events per 100,000 components, with 0.4 transfusion-related deaths occurring per 100,000 components [43]. Specifically, the risk of a hemolytic reaction due to ABO incompatibility is around 1:80,000, while the risk of a plasma incompatibility reaction is around 1:120,000 [42]. In emergency situations, the benefits of transfusion of group O donor blood to nongroup O recipients generally outweigh the low risks of transfusion reactions outlined above, particularly if low-titer anti-A/anti-B donors can be preferentially utilized [41]. Further, the study by Nessen et al. examining WB use in combat casualties revealed no increased risk of utilizing group O whole blood as a universal donor [39].

To prevent infectious disease spread during whole blood transfusion, all soldiers are prescreened prior to deployment and every 3 months during deployment. Rapid screening for hepatitis A, hepatitis B, and HIV is performed on donated blood, but no FDA-approved rapid screening tests exist, and the current tests are around 85% sensitive. Transfused units are routinely screened retrospectively in the United States, and transmission rates remain extremely low [44]. Spinella et al. noted that among 2831 samples retroactively tested, 0.11% were positive for hepatitis C and 0.07% were positive for human T-lymphotropic virus; no samples were positive for either HIV or hepatitis B [45]. The authors also found that there was no difference in the rates of disease transmission when comparing units that did or did not receive prescreening using rapid antigen testing prior to transfusion [45]. In military settings, where soldiers are frequently screened for blood-borne diseases, the ability to maintain a disease-free walking blood bank is relatively reliable, and the benefits of transfusion surpass the minimal risk of disease transmission. Civilians are not subject to the same screening requirements as soldiers. Creation of a walking blood bank among a civilian population would require careful selection of potential donors, the implementation of significant screening policies, and improved (and FDA-approved) rapid testing to evaluate whole blood samples prior to transfusion.

Current Guidelines

Point-of-Care Management

The majority of deaths secondary to hemorrhage among trauma patients occur within 24 h of injury, with the median time to death of around 2.7–3 h [26, 46]. This is particularly true in the austere or combat environment, where the majority of deaths occur in the prehospital environment or within 60 min of arrival at a forward treatment facility [47, 48]. As such, resuscitation should begin promptly and, in most cases, prior to the patient's arrival in a definitive care center. The Tactical Combat Casualty Care (TCCC) guidelines [2] detail the current military resuscitation methods and goals for point-of-care resuscitation. Published in 2014, these guidelines reflect a number of the advances previously discussed, including hypotensive resuscitation, the early use of blood products, and whole blood resuscitation in far-forward environments.

At point of injury, patients should be assessed for signs of hemorrhagic shock to determine if resuscitation is warranted. The two primary indicators of shock used in the field are the presence of altered mental status in a non-head-injured patient or the absence or diminution in the quality of the radial pulse. Casualties that do not have either of these findings on exam are most likely not in shock, and no resuscitation is provided. The recommended fluids for resuscitation according to TCCC guidelines, in descending order of priority, are whole blood; then a 1:1:1 ratio of plasma, platelets, and RBCs; then plasma alone; and finally RBCs alone. Hextend is the initial non-blood fluid recommended for resuscitation; LR and NS have the lowest priority. The resuscitation is continued until mental status and the radial pulse are restored and the casualty is moved as soon as is tactically feasible to a medical treatment facility for urgent surgical repair as needed. During transport, patients should continue to be resuscitated to 80–90 mmHg (and >90 mmHg in head-injured patients).

Civilian point-of-care resuscitation deviates slightly from the TCCC guidelines outlined above, though the same principles apply. Crystalloid, rather than colloid, will likely be the resuscitative fluid of choice when blood products are not available. Patients requiring resuscitation should be appropriately identified; EMS units contain blood pressure cuffs, and so a more accurate assessment of systolic blood pressure is possible. Some air evacuation units now carry blood products; [49, 50] if these products are available, the use of these products during transport is indicated. Whole blood, however, is not widely available in civilian populations at this time.

Definitive Resuscitation

Approaches to managing early resuscitation vary extensively among trauma centers in the United States [51]. The PROPPR trial convincingly demonstrated the benefits of high-ratio resuscitation in hemorrhaging trauma patients [26]. Yet high-ratio therapy alone is unable to address unique conditions in each patient that may be contributing to the development or persistence of coagulopathy. Therefore, definitive resuscitation should involve three components: first, initiation of empiric 1:1:1 therapy to temper the progression of coagulopathy; second, a rapid and accurate assessment of hemostatic mechanisms to characterize the patient's individual coagulopathy; and third, a transition to patient-specific resuscitation to definitively address the underlying coagulopathy.

Often, the most challenging element of definitive resuscitation is the rapid assessment of a patient's hemostatic capacity. Conventional coagulation tests, such as PT, PTT, international normalized ratio (INR), platelet count, and fibrinogen level, are substantially limited in two ways. First, the tests are time-consuming and often require 30–45 min to complete. The physiology of the patient can change substantially between the time when labs are drawn and the time when lab data is available. As a result, resuscitation based on these conventional tests lags behind any evolving coagulopathy. Second, the tests only examine a single element of coagulation in vitro rather than assessing the entire coagulation cascade in vivo.

Table 5.2 Thromboelastography parameters

Parameter	Measurement
Reaction rate (R value, R)	Quantity and quality of clotting factors
Kinetic time (K time, K)	Quantity and quality of clotting factors
α angle	Platelet and fibrinogen levels
Maximum amplitude (MA)	Overall clot strength (platelets + fibrinogen)
Lysis at 30 min (LY30)	Rate of fibrinolysis

Relevant thromboelastography (TEG) parameters to consider when managing resuscitation. Pathologic states such as acute traumatic coagulopathy (ATC) can produce derangements in multiple TEG parameters as ATC affects multiple components of primary and secondary hemostasis

A promising alternative to conventional coagulation testing is viscoelastic testing. Thromboelastography (TEG) and rotational thromboelastometry (ROTEM) dynamically assess hemostasis by applying a rotational force to a sample of whole blood and recording changes in clot strength over time [52]. The tests measure a number of different variables such as time to clot initiation, rate of clot formation, overall clot strength, and rate of fibrinolysis (see Table 5.2). A significant advantage to TEG/ROTEM is that both tests can be performed rapidly and at the bedside. Rapid TEG (r-TEG), a specific assay of TEG that uses both kaolin and tissue factor as reagents, can provide actionable information on a patient's clotting capacity within minutes.

TEG and ROTEM were initially developed for use in cardiac surgery but have recently gained traction as a feasible means of assessing hemostasis in trauma settings. Holcomb et al. compared r-TEG to conventional testing and found that r-TEG correlated well with conventional coagulation testing and was additionally more predictive of massive transfusion than either PT/INR or aPTT [53]. Other groups have independently shown that TEG/ROTEM values on admission are predictive of future blood product requirement [54–56] and the development of ATC [56].

Multiple centers have now demonstrated that TEG/ROTEM can be used to guide definitive resuscitative efforts. Gonzalez et al. [57] conducted a randomized clinical trial comparing massive transfusion directed by TEG to massive transfusion directed by traditional coagulation tests. In both groups, abnormal lab values resulted in specific transfusion interventions. The authors found that survival was higher in the TEG group than the conventional coagulation testing group ($p = 0.032$) and patients in the conventional coagulation testing group required more plasma and platelets in the first 2 h of resuscitation ($p = 0.022$ and $p = 0.041$, respectively) [57]. The authors concluded that TEG-guided massive transfusion was a more efficient and effective means of resuscitation than massive transfusion guided by conventional coagulation assays. Tapia et al. [58] retrospectively compared TEG-guided therapy to empiric 1:1:1 therapy in a similar demographic of patients requiring massive transfusion and found that 1:1:1 therapy actually worsened mortality in patients with penetrating trauma who required more than 10 units of RBCs [58]. Combined, these data suggest that TEG-guided therapy is superior to therapy guided by conventional coagulation testing and can be tailored to the individual patient in a manner that empiric therapy cannot replicate (see Fig. 5.4).

Definitive resuscitation unites empiric therapy and TEG-guided therapy. The two treatment modalities address two different elements: empiric therapy replaces what the patient is losing (whole blood) and temporizes the development of coagulopathy, while TEG-guided therapy corrects the specific coagulopathy. Empiric therapy with high-ratio 1:1:1 resuscitation should begin as close to the time of injury as possible. Once the source of hemorrhage is definitively controlled and the patient is no longer losing whole blood, TEG-guided therapy is warranted to address the residual coagulopathy [59]. Actively hemorrhaging patients typically reach the OR or the IR suite in a timely fashion; either of those areas can then serve as the "transition point" to more directed resuscitative care. The combination of these resuscitative paradigms allows for the flexibility needed to appropriately treat hemorrhagic shock.

Considerations in Blast-Injured Patients

Resuscitation in blast-injured patients must balance the goals of resuscitation with the specific pathologies of primary, secondary, and tertiary injury, the effect of the blast on systemic circulation, and the time elapsed from injury to treatment.

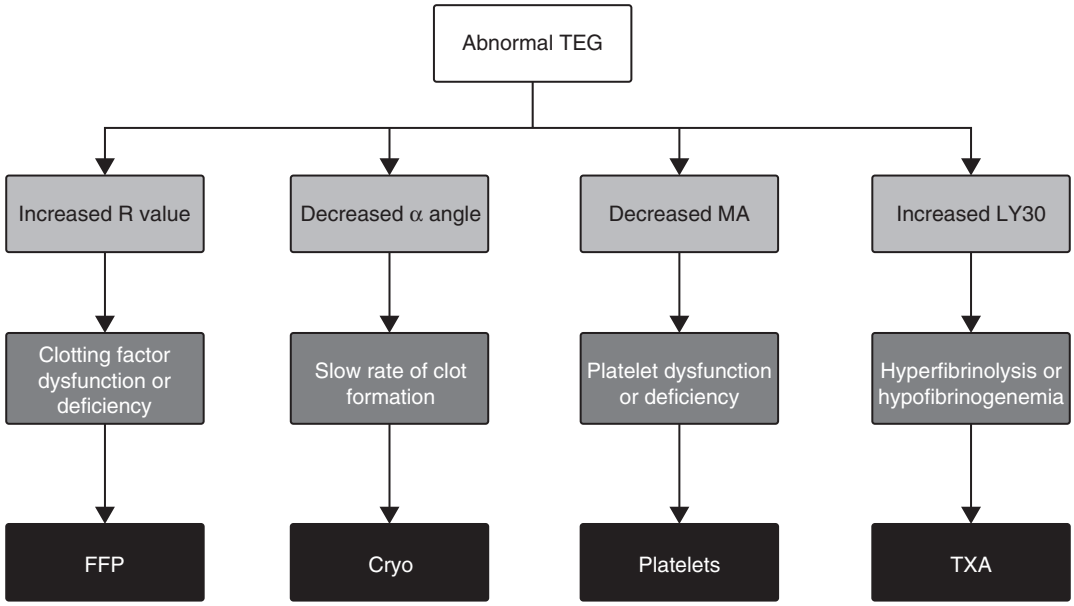

Fig. 5.4 Abnormal TEG parameters (blue) and potential therapeutic options (red). Of these, the most controversial is the management of a decreased LY30. TXA is part of resuscitation regimens at a number of institutions but must be given within 3 h of injury. ACA can be given if hyperfibrinolysis is detected later in the treatment course, but there is extremely limited data as to whether or not it provides survival benefit. FFP fresh frozen plasma, cryo cryoprecipitate, TXA tranexamic acid

Of particular concern in any blast-injured patient is primary injury to the lung as barotrauma represents a unique pathology not accounted for in the resuscitation literature described previously. Primary blast lung injury (PBLI) is due to a disruption of the alveolar septae with associated alveolar hemorrhage and impaired gas exchange [60]. PBLI typically manifests as pulmonary contusion with associated pneumothorax, pneumomediastinum, or tracheal injury. Patients with larger pulmonary contusions have a greater degree of respiratory compromise and often require mechanical ventilator support.

In any patient with PBLI, over-resuscitation should be carefully avoided as fluid overload in the setting of a compromised alveolar-capillary interface can quickly lead to pulmonary edema and acute respiratory distress syndrome (ARDS) [60]. Blood products should be preferentially administered over crystalloid in the setting of PBLI as the majority of a crystalloid transfusion will ultimately leave the intravascular space and exacerbate the underlying lung injury. Recent literature suggests that plasma helps to reconstitute the injured endothelium and glycocalyx following injury, while crystalloid causes further injury. This protective effect results in further reduction in third-spacing and reduced organ injury [61, 62]. To ensure that patients are not over-resuscitated, hypotension and volume status should be carefully assessed, and resuscitation should be guided by both the presence of coagulopathy and the intravascular volume deficit. As soon as the goals of resuscitation are achieved, patients with PBLI should be fluid restricted until PBLI resolves.

Resuscitation in patients with either secondary blast injury (penetrating injury) or tertiary blast injury (blunt injury) can closely follow the empiric 1:1:1 therapy described above. While therapy should be initiated as early as possible, suspicion for PBLI should remain high, and patients should be assessed as early as feasibly possible for occult pulmonary injury and impaired ventilation. However, under-resuscitation of these patients is equally, if not more, detrimental to survival. Patients with PBLI and secondary and tertiary injuries will have low oxygen-carrying capacity secondary to hemorrhage and impaired oxygenation and ventilation secondary to lung injury. Garner et al. used a swine blast/hemorrhage model to compare the effects of

hypotensive and normotensive resuscitation with NS in the setting of both blast injury and no blast injury [63]. The authors found that survival was significantly shorter in the hypotensive resuscitation group (~150 min) compared to the normotensive resuscitation group (~400 min; $p < 0.01$). The generalizability of this study is limited as the study used a non-survival model as well as NS as a resuscitation fluid. The findings should, however, underscore the importance of early resuscitation with blood products and the need for rapid definitive surgical control of bleeding followed by complete resuscitation.

Conclusion

Successful resuscitation should restore intravascular volume, buttress the hemostatic system, prevent coagulopathy, and maintain oxygen delivery and end-organ perfusion. Explosive injuries often produce substantial polytrauma and result in hemorrhagic shock, necessitating extensive resuscitative efforts. When possible, early resuscitation should focus on hypotensive resuscitation to maintain a low perfusion pressure without disrupting clot formation. Resuscitation with high-ratio component therapy (or whole blood, if components are unavailable) should begin en route to definitive care or upon arrival at a definitive care facility. After achieving hemorrhage control, TEG-guided therapy can be used (when available) to efficiently address the underlying coagulopathy likely present in these patients.

References

1. DePalma RG, Burris DG, Champion HR, Hodgson MJ. Blast injuries. N Engl J Med. 2005;352(13):1335–42.
2. Butler FK, Holcomb JB, Schreiber MA, et al. Fluid resuscitation for hemorrhagic shock in tactical combat casualty care: TCCC guidelines change 14-01--2 June 2014. J Spec Oper Med Peer Rev J SOF Med Prof. 2014;14(3):13–38.
3. Myburgh JA, Mythen MG. Resuscitation fluids. N Engl J Med. 2013;369(13):1243–51.
4. Bickell WH, Wall MJ Jr, Pepe PE, et al. Immediate versus delayed fluid resuscitation for hypotensive patients with penetrating torso injuries. N Engl J Med. 1994;331(17):1105–9.
5. Cohen MJ. Towards hemostatic resuscitation: the changing understanding of acute traumatic biology, massive bleeding, and damage-control resuscitation. Surg Clin North Am. 2012;92(4):877–91. viii.
6. Moss GS, Lowe RJ, Jilek J, Levine HD. Colloid or crystalloid in the resuscitation of hemorrhagic shock: a controlled clinical trial. Surgery. 1981;89(4):434–8.
7. Alderson P, Schierhout G, Roberts I, Bunn F. Colloids versus crystalloids for fluid resuscitation in critically ill patients. Cochrane Database Syst Rev. 2000;2:Cd000567.
8. Cannon WB, Fraser J, Cowell EM. The preventive treatment of wound shock. JAMA. 1918;70:618–21.
9. Bickell WH, Bruttig SP, Millnamow GA, O'Benar J, Wade CE. The detrimental effects of intravenous crystalloid after aortotomy in swine. Surgery. 1991;110(3):529–36.
10. Feinman M, Cotton BA, Haut ER. Optimal fluid resuscitation in trauma: type, timing, and total. Curr Opin Crit Care. 2014;20(4):366–72.
11. Eiseman B. Pulmonary effects of nonthoracic trauma. Introduction to conference. J Trauma. 1968;8(5):649–50.
12. Balogh Z, McKinley BA, Holcomb JB, et al. Both primary and secondary abdominal compartment syndrome can be predicted early and are harbingers of multiple organ failure. J Trauma. 2003;54(5):848–59. discussion 859-861.
13. Madigan MC, Kemp CD, Johnson JC, Cotton BA. Secondary abdominal compartment syndrome after severe extremity injury: are early, aggressive fluid resuscitation strategies to blame? J Trauma. 2008;64(2):280–5.
14. Kutcher ME, Howard BM, Sperry JL, et al. Evolving beyond the vicious triad: differential mediation of traumatic coagulopathy by injury, shock, and resuscitation. J Trauma Acute Care Surg. 2015;78(3):516–23.
15. Acute CMJ. Traumatic coagulopathy: clinical characterization and mechanistic investigation. Thromb Res. 2014;133(Suppl 1):S25–7.
16. Cohen MJ, Christie SA. New understandings of post injury coagulation and resuscitation. Int J Surg (Lond, Engl). 2016;33(Pt B):242–5.
17. Sondeen JL, Coppes VG, Holcomb JB. Blood pressure at which rebleeding occurs after resuscitation in swine with aortic injury. J Trauma. 2003;54(5 Suppl):S110–7.
18. Capone AC, Safar P, Stezoski W, Tisherman S, Peitzman AB. Improved outcome with fluid restriction in treatment of uncontrolled hemorrhagic shock. J Am Coll Surg. 1995;180(1):49–56.
19. Hampton DA, Fabricant LJ, Differding J, et al. Prehospital intravenous fluid is associated with increased survival in trauma patients. J Trauma Acute Care Surg. 2013;75(1 Suppl 1):S9–15.
20. Cotton BA, Reddy N, Hatch QM, et al. Damage control resuscitation is associated with a reduction in resuscitation volumes and improvement in survival in 390 damage control laparotomy patients. Ann Surg. 2011;254(4):598–605.

21. MacLeod JB, Lynn M, McKenney MG, Cohn SM, Murtha M. Early coagulopathy predicts mortality in trauma. J Trauma. 2003;55(1):39–44.
22. Brohi K, Singh J, Heron M, Coats T. Acute traumatic coagulopathy. J Trauma. 2003;54(6):1127–30.
23. Borgman MA, Spinella PC, Perkins JG, et al. The ratio of blood products transfused affects mortality in patients receiving massive transfusions at a combat support hospital. J Trauma. 2007;63(4):805–13.
24. Duchesne JC, Hunt JP, Wahl G, et al. Review of current blood transfusions strategies in a mature level I trauma center: were we wrong for the last 60 years? J Trauma. 2008;65(2):272–6. discussion 276-278.
25. Shaz BH, Dente CJ, Nicholas J, et al. Increased number of coagulation products in relationship to red blood cell products transfused improves mortality in trauma patients. Transfusion. 2010;50(2):493–500.
26. 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(5):471–82.
27. Duke MD, Guidry C, Guice J, et al. Restrictive fluid resuscitation in combination with damage control resuscitation: time for adaptation. J Trauma Acute Care Surg. 2012;73(3):674–8.
28. Guidry C, Gleeson E, Simms ER, et al. Initial assessment on the impact of crystalloids versus colloids during damage control resuscitation. J Surg Res. 2013;185(1):294–9.
29. Schreiber MA, Meier EN, Tisherman SA, et al. A controlled resuscitation strategy is feasible and safe in hypotensive trauma patients: results of a prospective randomized pilot trial. J Trauma Acute Care Surg. 2015;78(4):687–95. discussion 695-687.
30. Armand R, Hess JR. Treating coagulopathy in trauma patients. Transfus Med Rev. 2003;17(3):223–31.
31. Silliman CC, Clay KL, Thurman GW, Johnson CA, Ambruso DR. Partial characterization of lipids that develop during the routine storage of blood and prime the neutrophil NADPH oxidase. J Lab Clin Med. 1994;124(5):684–94.
32. Silliman CC, Voelkel NF, Allard JD, et al. Plasma and lipids from stored packed red blood cells cause acute lung injury in an animal model. J Clin Invest. 1998;101(7):1458–67.
33. Zallen G, Offner PJ, Moore EE, et al. Age of transfused blood is an independent risk factor for postinjury multiple organ failure. Am J Surg. 1999;178(6):570–2.
34. Zielinski MD, Jenkins DH, Hughes JD, Badjie KS, Stubbs JR. Back to the future: the renaissance of whole-blood transfusions for massively hemorrhaging patients. Surgery. 2014;155(5):883–6.
35. Spinella PC, Dunne J, Beilman GJ, et al. Constant challenges and evolution of US military transfusion medicine and blood operations in combat. Transfusion. 2012;52(5):1146–53.
36. Repine TB, Perkins JG, Kauvar DS, Blackborne L. The use of fresh whole blood in massive transfusion. J Trauma. 2006;60(6 Suppl):S59–69.
37. Manno CS, Hedberg KW, Kim HC, et al. Comparison of the hemostatic effects of fresh whole blood, stored whole blood, and components after open heart surgery in children. Blood. 1991;77(5):930–6.
38. Cotton BA, Podbielski J, Camp E, et al. A randomized controlled pilot trial of modified whole blood versus component therapy in severely injured patients requiring large volume transfusions. Ann Surg. 2013;258(4):527–32. discussion 532-523.
39. Nessen SC, Eastridge BJ, Cronk D, et al. Fresh whole blood use by forward surgical teams in Afghanistan is associated with improved survival compared to component therapy without platelets. Transfusion. 2013;53(Suppl 1):107s–13s.
40. Spinella PC, Perkins JG, Grathwohl KW, Beekley AC, Holcomb JB. Warm fresh whole blood is independently associated with improved survival for patients with combat-related traumatic injuries. J Trauma. 2009;66(4 Suppl):S69–76.
41. Berseus O, Boman K, Nessen SC, Westerberg LA. Risks of hemolysis due to anti-A and anti-B caused by the transfusion of blood or blood components containing ABO-incompatible plasma. Transfusion. 2013;53(Suppl 1):114s–23s.
42. Strandenes G, Berseus O, Cap AP, et al. Low titer group O whole blood in emergency situations. Shock (Augusta, Ga). 2014;41(Suppl 1):70–5.
43. Stainsby D, Jones H, Asher D, et al. Serious hazards of transfusion: a decade of hemovigilance in the UK. Transfus Med Rev. 2006;20(4):273–82.
44. Spinella PC, Pidcoke HF, Strandenes G, et al. Whole blood for hemostatic resuscitation of major bleeding. Transfusion. 2016;56(Suppl 2):S190–202.
45. Spinella PC, Perkins JG, Grathwohl KW, et al. Risks associated with fresh whole blood and red blood cell transfusions in a combat support hospital. Crit Care Med. 2007;35(11):2576–81.
46. Holcomb JB, del Junco DJ, Fox EE, et al. The prospective, observational, multicenter, major trauma transfusion (PROMMTT) study: comparative effectiveness of a time-varying treatment with competing risks. JAMA Surg. 2013;148(2):127–36.
47. Eastridge BJ, Mabry RL, Seguin P, et al. Death on the battlefield (2001-2011): implications for the future of combat casualty care. J Trauma Acute Care Surg. 2012;73(6 Suppl 5):S431–7.
48. Martin M, Oh J, Currier H, et al. An analysis of in-hospital deaths at a modern combat support hospital. J Trauma. 2009;66(4 Suppl):S51–60. discussion S60-51.
49. Jenkins D, Stubbs J, Williams S, et al. Implementation and execution of civilian remote damage control resuscitation programs. Shock (Augusta, Ga). 2014;41(Suppl 1):84–9.
50. Holcomb JB, Donathan DP, Cotton BA, et al. Prehospital transfusion of plasma and red blood cells in trauma patients. Prehosp Emerg Care Off J Natl Assoc EMS Phys Natl Assoc State EMS Dir. 2015;19(1):1–9.
51. 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(10):2478–86.
52. Whiting D, DiNardo JA. TEG and ROTEM: technology and clinical applications. Am J Hematol. 2014;89(2):228–32.
53. Holcomb JB, Minei KM, Scerbo ML, et al. Admission rapid thrombelastography can replace conventional coagulation tests in the emergency department: experience with 1974 consecutive trauma patients. Ann Surg. 2012;256(3):476–86.
54. Plotkin AJ, Wade CE, Jenkins DH, et al. A reduction in clot formation rate and strength assessed by thrombelastography is indicative of transfusion requirements in patients with penetrating injuries. J Trauma. 2008;64(2 Suppl):S64–8.
55. Kornblith LZ, Kutcher ME, Redick BJ, Calfee CS, Vilardi RF, Cohen MJ. Fibrinogen and platelet contributions to clot formation: implications for trauma resuscitation and thromboprophylaxis. J Trauma Acute Care Surg. 2014;76(2):255–6. discussion 262-253.
56. Hagemo JS, Christiaans SC, Stanworth SJ, et al. Detection of acute traumatic coagulopathy and massive transfusion requirements by means of rotational thromboelastometry: an international prospective validation study. Crit Care. 2015;19:97.
57. 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(6):1051–9.
58. Tapia NM, Chang A, Norman M, et al. TEG-guided resuscitation is superior to standardized MTP resuscitation in massively transfused penetrating trauma patients. J Trauma Acute Care Surg. 2013;74(2):378–85. discussion 385-376.
59. Kemp Bohan PM, Yonge JD, Schreiber MA. Update on the massive transfusion guidelines on Hemorrhagic shock: after the wars. Curr Surg Rep. 2016;4(5):16.
60. Argyros GJ. Management of primary blast injury. Toxicology. 1997;121(1):105–15.
61. Holcomb JB, Pati S. Optimal trauma resuscitation with plasma as the primary resuscitative fluid: the surgeon's perspective. Hematology Am Soc Hematol Educ Program. 2013;2013:656–9.
62. Kozar RA, Peng Z, Zhang R, et al. Plasma restoration of endothelial glycocalyx in a rodent model of hemorrhagic shock. Anesth Analg. 2011;112(6):1289–95.
63. Garner J, Watts S, Parry C, Bird J, Cooper G, Kirkman E. Prolonged permissive hypotensive resuscitation is associated with poor outcome in primary blast injury with controlled hemorrhage. Ann Surg. 2010;251(6):1131–9.