# Damage control resuscitation in adult trauma patients: What you need to know

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ABSTRACT: Death after injury is a worldwide epidemic. Hemorrhage as a cause of death represents the leading potentially preventable condition. Based on hard-won experience from the recent wars, and two decades of military and civilian research, damage-control resuscitation (DCR) is now widely used. This article will briefly describe the history of blood transfusion, outline "why we do DCR," and then discuss "how we do DCR." Modern DCR occurs both prehospital and in the hospital and has several main tenants. Currently, DCR focuses on the liberal use of temporary hemorrhage-control adjuncts, early use of whole blood or balanced blood product-based transfusions, mitigation of crystalloid use, hypotensive resuscitation to promote hemostasis and decrease coagulopathy, and correction of ongoing metabolic derangements, followed by rapid definitive hemorrhage control. These concepts have evolved from a series of lessons learned over time from both civilian and military trauma casualties, and DCR is now the standard of care in trauma resuscitation. (J Trauma Acute Care Surg. 2023;95: 464–471. Copyright © 2023 Wolters Kluwer Health, Inc. All rights reserved.)

KEY WORDS: Damage Control Resuscitation; Transfusion; Whole Blood; Hemorrhagic Shock; Traumatic Coagulopathy.

### **DAMAGE-CONTROL RESUSCITATION**

Trauma is a leading cause of morbidity and mortality worldwide. <sup>1</sup> Death secondary to hemorrhage represents a potentially preventable ailment that has garnered significant clinical and research attention over the last two decades. The principles governing damage-control resuscitation (DCR) embody a series of strategies and techniques centered on the mitigation of morbidity and mortality for traumatically injured patients in hemorrhagic shock.<sup>2–4</sup> In its current form, DCR focuses on the early use of whole blood or balanced blood product-based transfusions, mitigation of crystalloid use, early hemorrhage control, hypotensive resuscitation to promote hemostasis, decrease coagulopathy, correction ongoing metabolic derangements, followed by rapid definitive hemorrhage control.<sup>2</sup> These concepts have evolved from a series of lessons learned over time from both civilian and military trauma casualties and have emerged as the standard of care in trauma resuscitation.

#### WHY WE DO IT

## **History of Blood Product-Based Resuscitation**

The earliest accounts of blood transfusion date back to 1666 when Richard Lower demonstrated that transfusing canine blood was lifesaving (Fig. 1).<sup>5</sup> This concept was extrapolated to humans and in 1667 Jean Baptiste Denis and Lower transfused ovine blood in efforts to cure a patient suffering from mental illness.<sup>5</sup> This proved unsuccessful and the practice of blood trans-

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fusion was subsequently not studied again throughout Europe until the 1800s.

Following the identification that blood was species-specific, the first human-to-human transfusion was performed by Blundell<sup>6</sup> in 1818. The first accounts of whole blood transfusions in combat scenarios occurred in 1864.7 Subsequently, Robertson<sup>8–10</sup> described the early method of modern blood collection techniques and storage in World War I (WWI) where he collected blood into glass bottles, cooled it on ice for storage, and administered transfusions to wounded soldiers on the frontlines. Concurrently, Robertson<sup>10</sup> urged that whole blood transfusions be more frequently employed as he felt that blood transfusions offered the potential to carry patients over a critical period of illness. One hundred years following the first human-to-human transfusion, the United States Army Medical Department adopted citrated whole blood transfusions into practice to help combat shock for the American Expeditionary Forces in 1918. 10 During World War II (WWII), central civilian blood collection sites emerged and dried plasma and whole blood transfusions were agreed upon as the ideal treatment for shock wherever possible, as well as patient warming to prevent hypothermia, and assurance of adequate analgesia. <sup>5,11,12</sup> Post-WWII, whole blood transfusions continued during the Korean War, however it was felt that many of the lessons learned regarding the benefits of whole blood transfusion from WWI and WWII were forgotten as there was a tendency to transfuse alternative solutions, such as plasma expanders. 5,12 Whole blood, as well as blood components and crystalloid solutions, were all used during the Vietnam War and in 1971, Miller et al. 13 were the first to describe the acute coagulopathy of trauma. Per their account, they suggested that this pathology was unsuccessfully treated with plasma and ongoing bleeding could only be mitigated when whole blood was used.

As time progressed, these lessons learned from combat trauma were forgotten, and the use of whole blood and blood products was replaced by alternative resuscitation solutions. The civilian adoption of large volume crystalloid transfusions became commonplace following Shires et al.'s 14 1973 study that

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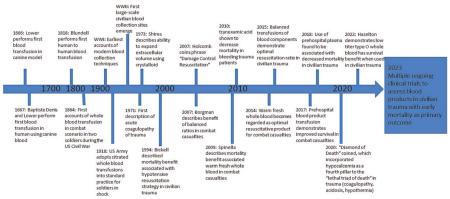


Figure 1. Evolution of resuscitation from 1666 to 2023.

demonstrated an ability to restore extracellular fluid volumes by administering crystalloid solutions in volumes three times the suspected blood loss. Ubiquitous utilization of crystalloid was driven by the ATLS guidelines, which propagated the early administration of two liters of crystalloid fluids followed by blood component therapy for those who were still actively bleeding after their initial crystalloid administration. Moreover, concomitant fears over contracting transmittable diseases, such as hepatitis C and human immunodeficiency Virus through blood product transfusions lead to large volume crystalloid-based resuscitation practices becoming the standard civilian practice throughout the 1990s. 5,12

Crystalloid administration, which can only improve blood flow dynamics via volume expansion to augment cardiac output, fails to improve the oxygen carrying capacity of the blood. While increasing the cardiac output can help initially increase oxygen delivery, replacement of active hemorrhage with solutions not capable of carrying oxygen ultimately worsens ischemic insult at the cellular level where oxygen debt is present. This is due to the dilutional effect within the blood which decreases the overall oxygen carrying content and predisposes patients to ischemia reperfusion injury, edema, multiorgan failure, and death. 16 Compounding this, large-volume crystalloid administration has been found to worsen systemic acidosis and create an ongoing dilutional coagulopathy further increasing critical organ damage. 17,18 Both prehospital and hospital use of crystalloid, and not blood products, are associated with multiple inflammatory complications, including ARDS. <sup>19,20</sup> These findings, along with the propensity to induce hypothermia secondary to the rapid administration of nonwarmed fluids, represent an iatrogenic resuscitation injury and the accelerates the "lethal triad of death" (i.e., coagulopathy, acidosis, and hypothermia).

#### Birth of DCR

Recognizing the counterproductive nature of large volume crystalloid-based resuscitation for critically ill trauma patients in hemorrhagic shock paved the way for the development of a new resuscitation strategy that focused on promoting hemostasis by preventing coagulopathy, acidosis, hypothermia, and ischemia. Damage-control resuscitation, a term coined by Holcomb et al. in 2007, represented a strategy that was introduced to work synergistically with damage control surgery (DCS) during the initial phases of Operation Iraqi Freedom and Operation Enduring Freedom.<sup>2</sup> While DCS aims to obtain rapid control of ongoing hemorrhage and contamination, the goal of DCR is to address

and mitigate the effects of the entire lethal triad of death through early temporary hemorrhage control, minimize crystalloid and a balanced blood product-based resuscitation strategy. <sup>2,21</sup> The high combat casualty rate early during Operation Iraqi Freedom and Operation Enduring Freedom, where access to large volumes of blood products was readily available, provided a sizable cohort of patients that benefited from these practices in a short period of time. Using blood components in a balanced fashion was associated with improved outcomes after massive transfusion in military casualties. <sup>3</sup> Damage-control resuscitation quickly became the standard resuscitation practice for military combat operations.

The rapid initiation of DCR for combat casualties in extremis focused initially on these main principles: rapid control of bleeding, limiting ongoing resuscitation to maintain a systolic blood pressure of approximately 90 mm Hg, a concept termed hypotensive resuscitation, and restoration of intravascular volume using thawed plasma and packed red blood cells as primary resuscitation fluids with a ratio of 1:1 or 1:2, with early use of platelets and cryoprecipitate and whole blood, while limiting crystalloid.<sup>2</sup> Subsequently a series of civilian studies demonstrated that transfusion of higher ratios of plasma/red blood cells and plasma/platelets targeting a balanced resuscitative comprised of equal amounts of plasma, packed red blood cells, and platelets represented the ideal blood component-based strategy.<sup>2</sup> These principles proved to decrease the amount of intraoperative coagulopathic bleeding and allowed surgeons a greater chance for operative success in controlling surgical hemorrhage. Furthermore, due to a focus on early and aggressive initiation of blood products with DCR, patients frequently were found to arrive to the intensive care unit in the postoperative period normothermic, euvolemic, non-acidotic, and without evidence of ongoing coagulopathy.<sup>25</sup>

#### **Incorporating Whole Blood**

As military conflicts progressed, and balanced resuscitation became the norm, the utilization of warm fresh whole blood (WFWB) as the initial resuscitation fluid became more prevalent due to its ability to be rapidly obtained from "walking blood banks." Walking blood banks used prescreened military personnel within the combat zone to act as on-demand blood donors during times of need. As such, these donations were not processed or separated into components. In multiple studies, WFWB in the combat settings was found to be independently associated with improved outcomes and decreased mortality

rates when compared with component-based resuscitation strategies. <sup>26–29</sup> As these data became known, the Tactical Combat Casualty Care Committee officially recommended WFWB as the optimal prehospital resuscitative product for combat casualties in hemorrhagic shock in 2014. <sup>30</sup> Subsequently, the Department of Defense (DoD) has recommended that whole blood is the optimal resuscitative fluid across the entire battlefield. <sup>31</sup>

While WFWB is an excellent resuscitation fluid, it is not Food and Drug Administration (FDA) cleared. Conversely, low titer type O whole blood (LTOWB), which represents a FDA cleared whole blood product, offers the benefit of being more concentrated than blood component therapy, has an improved oxygen carrying capacity when compared with packed red blood cells, and offers an improved coagulation profile compared with fresh frozen plasma.<sup>32</sup> Low titer type O whole blood is an inherently balanced product making it more user-friendly than component-based strategies. Moreover, whole blood represents a logistically easier construct as it only requires refrigeration, as opposed to component therapy which requires refrigeration, freezing, and the platelet agitation. In military settings, service members are screened in the predeployment period for their blood group and anti-A and anti-B antibody titer levels. Those who are type O with antibody titers less than 1:256 are regarded as universal whole blood donors and represent an ideal donor for walking blood banks when emergently required.<sup>32</sup> Utilization of WFWB is not currently approved by the FDA and therefore in the United States is only used in the deployed setting for life threatening injuries when alternatives are not readily available.<sup>33</sup>

As opposed to WFWB, LTOWB blood transfusions have been recently incorporated into the civilian setting, with up to 50% of civilian trauma centers using this product. The cold storage process of LTOWB effectively increases the shelf life of whole blood to either 21 or 35 days depending on the preservation solution when compared with WFWB, which must be used within 24 hours from collection. 32-35 However, the storage and preservation process for cold stored LTOWB required by the US FDA for civilian use is felt by many to decrease the hemostatic benefits that have been demonstrated with WFWB in combat settings. Despite this, Hazelton et al.36 demonstrated in a large multicenter observational study that the utilization of cold stored LTOWB for civilian trauma was associated with a decreased risk of mortality (odds ratio, 0.52; p < 0.01) and bleeding complications (odds ratio, 0.91; p < 0.01) when compared with those who only received blood component therapy. Whether it be cold stored LTWOB in the civilian setting or either LTOWB or WFWB in the deployed combat environment, incorporation of whole blood into DCR has become increasingly popular and represents a product more similar with shed blood when compared with blood component therapy plus crystalloid. Despite the adoption of WFWB and LTOWB in the military and civilian setting and its strong physiologic rationale for use, a definitive prospective, randomized controlled trial within the civilian setting assessing the utility of cold stored LTOWB should start enrolling patients soon (Trauma Resuscitation With Low-Titer Group O Whole Blood or Products - Full Text View—ClinicalTrials.gov).

### **Prehospital Blood Products**

A main tenant of DCR, as previously described, is the early utilization of blood products as the primary resuscitation fluids.

Colloid and crystalloid infusions have traditionally been administered in the prehospital setting due to their logistical ease of use and low cost. Given the recent data on increased complications with crystalloids, blood product administration in the prehospital period is a topic of great interest within the trauma community.

Focused efforts within both the military and civilian sectors have resulted in blood products, both separate blood product components and whole blood, being incorporated into prehospital care. Similarly, despite the resource limited nature of the forward deployed military setting, prehospital blood transfusion by military providers is common. Multiple accounts within the combat environment have demonstrated safety with prehospital blood component transfusions, as well as an independently associated mortality benefit with its use, especially when used early after injury.<sup>37–39</sup> Civilian studies, on the other hand have not been as consistent in their results. Numerous studies suggest that there may be a reduction in mortality, however evidence to date varies.

The landmark multicenter randomized Prehospital Air Medical Plasma Trial (PAMPer) demonstrated a significant improved 30-day mortality in patients who received two units of plasma, in addition to standard treatment, during their prehospital en-route care. 40 Secondary analysis demonstrated that any prehospital blood product yielded a survival advantage compared with crystalloid therapy and those who received prehospital packed red blood cells plus plasma had the greatest survival benefit. 41 Conversely, the single center Control of Major Bleeding After trauma Trial (COMBAT), failed to demonstrate a 28-day mortality benefit between those transfused prehospital plasma and those who were not. 42 Subsequently, the UK-based multicenter Resuscitation with Pre-Hospital Blood Products Study (RePHILL) failed to demonstrate a significant difference in their primary outcomes between those transfused with prehospital packed red blood cells and lyophilized plasma versus normal saline. 43 Based on the differences in trial design, patient populations, administered blood products, and outcomes assessed, PAMPer, COMBAT, and RePHILL highlight that different systems of care and study design can affect outcomes. At this point relatively few prehospital systems are transfusing blood prehospital, a major impediment is the lack of reimbursement. 44 Despite the lack of consistent results across studies, prehospital blood product transfusions are currently considered to be best practice recommendations by the Trauma, Hemostasis, and Oxygenation Research and American Association of Blood Banks Working Party.<sup>45</sup>

The utilization of whole blood in the prehospital setting represents a more feasible option compared to blood components due to inherently providing an automatic balanced transfusion, ability to provide prehospital platelets inherent within whole blood, and an ability to mitigate the need for thawing of plasma. Despite the military's 2014 JTS CPG recommending whole blood to be the optimal prehospital fluid for hemostatic resuscitation, data supporting its use in military settings are currently limited to case series and retrospective findings. <sup>30,37–39</sup> Civilian data using early transfusions of cold stored LTOWB in the prehospital setting suggests that prehospital LTOWB is safe, may be associated with hemostatic benefits, is associated with greater improvements in shock physiology, and may be associated with decreased early mortality. <sup>46,47</sup> Taken together, while whole blood in the prehospital setting is appealing and appears safe, the definitive trial has just recently started enrolling patients, (Type O

Whole Blood and Assessment of Age During Prehospital Resuscitation Trial - Full Text View - ClinicalTrials.gov)

#### **Adjuncts for DCR**

In addition to the blood products, early use of tourniquets and hemostatic dressings has been widely implemented, and associated with improved outcomes. 48-52 Additionally, various pharmacologic agents have been incorporated into resuscitative practices. While combatting the lethal triad of coagulopathy, acidosis, and hypothermia was the original goal behind DCR, recent evidence suggests that hypocalcemia remains an integral component during early trauma resuscitation. As such, hypocalcemia has recently been incorporated into the lethal triad of death giving way to what is referred to now as "the diamond of death." 53 While traditional teaching states that hypocalcemia within trauma is a result of the citrate solution with blood products, recent evidence suggests that many trauma patients are actually deficient in calcium prior to the initiation of any blood products. This hypocalcemic state was found to be associated with the need for ongoing transfusions, increased risk for massive transfusion, and higher mortality rates.<sup>53</sup> Although there are no specific guidelines for civilian practice on the timing and degree of calcium supplementation, current military guidelines recommend the administration of calcium for patients in hemorrhagic shock.<sup>54</sup>

Hyperfibrinolysis represents a unique coagulopathy phenotype displayed by a subset of patients that has been associated with poor outcomes. Tranexamic acid (TXA), an antifibrinolytic agent that acts as a lysine receptor antagonist on plasminogen to block fibrinolysis, has demonstrated a significant decrease in mortality for civilian traumas when administered within 3 hours of injury. Data from military trauma patients have been congruent with civilian data and indicate increased survival rates with early administration of TXA for patients at risk for hemorrhagic shock. As such, many civilian guidelines recommend the administration of a 1-g TXA bolus within 3 hours from injury followed by another 1-g infusion of TXA over 8 hours. However, some civilian systems and the DoD have deployed a simpler dosing regimen (2 g for patients with traumatic brain injury and/or hemorrhagic shock), based on results from Rowell et al.

Fibrinogen deficiency can occur early during the resuscitative period and has been intimately linked to the degree of shock and tissue injury a patient experiences.<sup>61</sup> Low fibrinogen levels have been previously shown to be associated with the need for ongoing massive transfusion and increased mortality risk.<sup>62</sup> Because of this, cryoprecipitate, a pooled blood product that contains fibrinogen, factor VIII, factor XIII, Von Willebrand factor, and fibronectin, has been included into many centers as a part of their massive transfusion protocol or as a supplement for hypofibrinogenemia. Previous findings suggest that there is a wide degree of practice patterns surrounding cryoprecipitate transfusions and the optimal timing of replacement, transfusion strategy, and transfusion thresholds continue to remain an active area of research.<sup>63</sup> Cryoprecipitate, in combination with fresh frozen plasma, has proven superior to fresh frozen plasma alone for rapid correction of hypofibrinogenemia, which remains in line with the fibringen concentrations within cryoprecipitate compared with fresh frozen plasma (8–16 g/L vs. 2 g/L).<sup>64</sup> While cryoprecipitate represents the standard approach for fibrinogen replacement in the United States, the utilization of fibringen concentrates, which

offer a higher concentration of fibrinogen than cryoprecipitate (20 g/L vs. 8–16 g/L), represents the approach in Europe. Innnerhofer et al., demonstrated superior reversal of trauma induced coagulopathy with fibrinogen concentrate compared with plasma and suggest that early fibrinogen supplementation may translate into improved outcomes. Results from a large, randomized study powered to assess fibrinogen replacement with cryoprecipitate with regards to trauma-specific outcomes will soon be available (Early Use of Cryoprecipitate With Major Hemorrhage Protocol (MHP) Activation - Full Text View - ClinicalTrials.gov).

While various studies have suggested the benefit of adding fibrinogen concentrate as a more condensed replacement strategy compared with cryoprecipitate or fresh frozen plasma, utilization of prothrombin complex concentrate (PCC) has garnered recent interest as a resuscitation adjunct in efforts to rapidly replete factors II, VII, IX, and X.<sup>67</sup> PCC represents a highly concentrated solution of factors II, VII, IX, X, proteins C and S, antithrombin III, and heparin that has traditionally been used to rapidly correct warfarin-induced coagulopathy; however, recent reports suggest it may help promote hemostatic resuscitation.<sup>67</sup> Retrospective studies suggest that the utilization of PCC as an adjunct to standard resuscitation practices may be associated with decreased transfusion requirements, acute respiratory distress syndrome, acute kidney injury, and improved survival rates without any evidence of increased risk of thromboembolic events.<sup>67</sup> Conversely, the PROCOAG Randomized Clinical Trial failed to demonstrate a difference in 24-hour blood product requirements between trauma patients resuscitated with PCC as a hemostatic adjunct versus those who were not. 68 While PROCOAG failed to demonstrate support for the systematic use of PCC, the endpoint was confounded by survival bias and the product used may differ in efficacy from other PCCs. An 8000 subject multicenter randomized clinical trial assessing PCC use in trauma is currently enrolling patients and should provide definitive answers toward its utility after traumatic hemorrhagic shock (Evaluation of BE1116 in Patients With Traumatic Injury and Acute Major Bleeding to Improve Survival (TAP Study) - Full Text View - ClinicalTrials.gov).

Finally, despite traditional teaching suggesting there is no role for vasoactive medications in hemorrhagic shock, this has been questioned recently as refractory vasodilatation represents the final phase in all forms of decompensated shock. Understanding that hemorrhagic shock can alter neurohormonal function resulting in a vasopressin-depleted state despite ongoing blood product replacement, Sims et al.<sup>69</sup> assessed the addition of low dose vasopressin into their resuscitation strategy. They found that incorporation of vasopressin during the acute resuscitative period decreases overall blood product requirements and actually decreased rates of deep venous thrombosis despite vasopressin use being associated with enhanced platelet function. Despite the fact that the addition of vasopressors may help augment a physiologically depleted state and overcome refractory vasoplegia, data surrounding these concepts are limited and vasopressor administration during hemorrhagic shock is only currently recommended by European guidelines.<sup>60</sup>

### **Time to Hemorrhage Control**

Experience in both military and civilian trauma care have shown that faster transport combined with effective prehospital

hemorrhage control interventions and blood transfusion improves the outcomes of patients suffering hemorrhagic shock. <sup>37,40,41</sup> Outcomes of military casualties with hemorrhagic shock have improved with widespread use of tourniquets and early balanced transfusion therapy. <sup>52</sup> Conversely, only recently have some civilian trauma systems deployed all these interventions, despite the recognition that time to hemostasis (usually recorded in hours after injury) is a critical determinate of survival. <sup>70–72</sup> While this paper is focused on "why and how we do it" the importance of rapid transport combined with prehospital hemorrhage control and balanced blood transfusion is becoming clear. Irrespective of the modality, preoperative temporary truncal and extremity hemorrhage control combined with blood transfusion should offer the best possibility of improving patient outcomes after severe injury.

#### How We Do It

Institutional guidelines for the management of hemorrhagic shock vary depending on the resources and expertise available. As such, the practice patterns described below and in Figure 2 are intended to act as a reference point for how our group performs DCR at a high volume, American College of Surgeons Level I trauma center. Our group has had a long term relationship with the military and these principles represent our implementation of military and civilian lessons learned over the last 20 years. 73

Prior to patient arrival it is optimal that a well-defined communications system is in place to facilitate communication between the prehospital providers and the trauma team. This helps to identify patients at risk for hemorrhagic shock, those already in hemorrhagic shock (and receiving blood), and alerts the team to any changes in patient status prior to arrival. A number of emergency medical services crews that transport patients to our facility transfuse prehospital blood products. As such, we encourage the liberal use of prehospital component therapy or LTO + WB for patient's currently in or displaying risk factors for hemorrhagic shock.

Upon arrival to the trauma bay, the patient's primary and secondary surveys are rapidly completed in accordance with American Trauma Life Support principles. Because early identification of those in hemorrhagic shock or those at risk for developing hemorrhagic shock remains crucial toward having a successful resuscitation, rapidly controlling external hemorrhage, obtaining a patient's heart rate and blood pressure, assessing for alterations in mentation, performing a rapid Focused Assessment with Sonography in Trauma examination, and assessing chest and pelvic radiographs remains critical. In our practice, blood transfusions are liberally initiated with signs of ongoing bleeding, hemodynamic instability or clinical gestalt. During the evaluation multiple intravenous access sites are obtained. If peripheral intravenous lines cannot be rapidly obtained, early use of intraosseous access facilitates blood transfusion. Central access can be obtained via the introduction of a large bore sheath for rapid transfusion of warm products. For those patients with suspected abdominopelvic trauma, we make all attempts to obtain central access via the subclavian veins when needed in order not to interfere with cervical collar placement and mitigate the risk of transfusing blood products directly into potentially damaged vasculature within the abdomen and pelvis.

Our initial laboratory tests during the resuscitation include an arterial blood gas and thromboelastography (TEG), along with the other standard laboratory tests. We use the arterial blood gas to help us assess the degree of shock present on arrival and the patient's overall metabolic state based off their pH, bicarbonate, base deficit, and lactate. Although TEG values are not used during the initial resuscitation, we correct any coagulopathy evident on TEG following presumed control of ongoing hemorrhage.

Once appropriate intravenous access has been obtained and in patients with evidence of hemodynamic instability or concerns for ongoing bleeding, we initiate resuscitative efforts using blood products via activating our massive transfusion protocol. At our institution we currently use both LTO + WB whole blood (for all patents irrespective of age and sex), and standard blood

#### Physical exam Send labs Physical exam · Vital signs • Rapidly To OR and/or IR · Vital signs • IV or IO Access • FAST exam • Intubation (low TV) · Minimal crystalloid · Start Blood (WB or · CFA arterial line balanced components) Compressible · Minimal crystaloid hemorrhage control with • Hypotensive Resuscitation · Other hemostatic appropriate Devices • Central Access adjuncts as indicated · Start Blood (WB or (REBOA, etc) · External hemorrhage balanced components) control with appropriate After hemostasis Hypotensive resuscitation acheived, component devices • C-Collar for blunt patients • CXR/Pelvis X-ray / Other tranfusion based on lab **Imagining** Pelvic binder • Decompress chest as indicated Pelvic binder

**Figure 2.** Flow of DCR for a "typical" patient. The flow of diagnostic modalities and interventions that should occur when using the DCR approach for severely injured patients suffering hemorrhagic shock. Many of these will occur simultaneously, depending on your local trauma team. Likewise the location of these interventions will vary based on your site specific capabilities, logistics and new technology. IV, intravenous; IO, intraosseous; C-Collar, cervical collar; FAST, focused assessment with sonography for trauma; CXR, chest x-ray; OR, operating room; IR, interventional radiology; TV, tidal volume; CFA, common femoral artery; REBOA, resuscitative endovascular occlusion of the aorta.

component therapies. <sup>74,75</sup> Prior to patient arrival if there is any concern that the patient may warrant blood products based on the prehospital information provided, either a cooler of whole blood or an "ED Quick Pack" cooler is called for. Our ED Quick Pack coolers are individual coolers stored with the trauma bay that contain two units of PRBCs and 2 units of fresh frozen plasma. These can be rapidly called for and are ready for emergent release. Our center also carries LTO + WB that can be released via attending discretion for patients at risk of requiring massive transfusion. While the ED Quick Packs are located within the trauma bay, our emergent release LTO + WB coolers, which contain four units of LTO + WB, are physically stored at a nearby satellite blood bank and can be accessed in a rapid fashion. Whole blood refrigerators have been strategically placed within the trauma bay to decrease the time to whole blood access.

Blood product components or LTO + WB via the ED Quick Pack are transfused at the earliest time possible. Our goal and resuscitative focus for all traumatically injured patients is to initiate blood-based resuscitation as soon as possible with the goal of completely eliminating any crystalloid use for patients in suspected hemorrhagic shock. <sup>76</sup> We prefer to use LTO + WB for the presumed sickest patients in efforts to limit this resource to the patients that we believe may benefit the most from it. In addition, we endorse the principles of hypotensive resuscitation, targeting a systolic blood pressure no greater than 90 mm Hg and appropriate mentation, when clinically feasible. Nevertheless, circumstances concerning for ongoing hemorrhage, either internally or externally, typically prompt early transfusion regardless of the systolic blood pressure to proactively resuscitate these patients and prevent hemodynamic collapse.

All patients who have had the massive transfusion protocol activated receive 2 g of TXA via intravenous or intraosseous routes (if not received prehospital) if they present within 3 hours from injury. After patients receive their first two units of blood products, 2 g of calcium are preemptively given to combat any presenting hypocalcemia and mitigate the risks associated with the citrate solutions within the individual blood products. To date, we currently do not routinely encourage the use of intravascular hemostatic adjuncts such as PCC; however, our institution is involved in multiple randomized studies, including the randomized project evaluating PCC in the early resuscitative period for patients in hemorrhagic shock. Moreover, we currently do not endorse the use of vasopressors early within the resuscitative period. While ongoing research may eventually support this practice as a method to overcome trauma induced vasoplegic states, we tend to abide by the principle of replacing shed blood with blood products to assure an adequate resuscitative status. We do recognize, however, that various injury patterns, especially those with a neurogenic component, may require the eventual use of vasopressors and support their use during these scenarios once we think hemorrhage control has been obtained.

While we think the early use of blood products, mitigation of crystalloid use, practice of hypotensive resuscitation, hypothermia prevention and early calcium replacement remains critical, rapid and definitive hemorrhage control represents the most important aspect of all these principles. It is clear that without rapid and definitive hemorrhage control, resuscitation is unduly prolonged and successful outcomes remain near impossible. Therefore, an early and important focus of ours is the immediate

identification of the source of hemorrhage, mitigation of time spent in the trauma bay, and expedited transport to the operating room or interventional radiology suite. Here, the principles of damage-control surgery are employed while the ongoing DCR resuscitative efforts that were started prehospital are continued throughout the hospital. As others have found, as DCR principles are implemented, DCS and open abdomens becomes much less common. All efforts are made to use LTOWB or balanced blood product transfusions comprised of equal amounts of packed red blood cells, fresh frozen plasma, platelets and cryoprecipitate by our trauma anesthesia group who continues the resuscitative efforts within the operating room.

Following definitive hemorrhage control, the resuscitation is usually fairly straightforward, and completed in the postoperative period. We guide our component resuscitation strategy based on serial laboratory and physiologic markers for hypovolemia, again avoiding crystalloid. Transfusion is continued to maintain appropriate blood volume, perfusion, and delivery of oxygen. As mild postoperative coagulopathies are not uncommon following hemorrhagic shock, we trend patient's TEG values and will correct any ongoing deficiencies with component therapy to mitigate the risk for trauma induced coagulopathy. Given the emerging data on trauma induced endotheliopathy, plasma and not crystalloid is frequently used to restore intravascular volume and repair the glycocalyx. <sup>77</sup> Our goal is to limit total crystalloid volume to 2 L for 24 hours in these critically injured and massively transfused patients. Once hemodynamic stability has been assured, ongoing coagulopathies have been corrected, and the patient's shock physiology has been reversed, de-resuscitative efforts are initiated to mitigate overresuscitation within the intensive care unit.

Finally, it is sometimes difficult to follow all that happens in a complicated resuscitation. Therefore, based our guidelines all these interventions are tracked in a robust performance improvement system, allowing rapid loop closure.

#### **CONCLUSION**

Damage-control resuscitation represents a paradigm changing practice for trauma patients in hemorrhagic shock. The principles of early blood product utilization, mitigation of crystalloid use, early hemorrhage control, and hypotensive resuscitation, in combination with damage-control surgery, have successfully been deployed in both military and civilian environments. While the trauma community has made many advances in recent history with regards to resuscitative efforts, and in some ways come full circle with our resuscitative practices (i.e., incorporation of whole blood), research into the optimal resuscitative strategy is still needed to help elucidate the best practice patterns for patients in hemorrhagic shock. Bleeding patients are still dying, thus continued efforts in this arena should remain a top research priority to help mitigate potentially preventable deaths from hemorrhagic shock.

#### **AUTHORSHIP**

D.T.L. drafted the article and J.B.H. edited the article. Both authors reviewed, edited, and approved the article prior to final submission.

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#### **DISCLOSURE**

D.T.L. has no conflicts to disclose. J.B.H. is on the board of directors of Decisio Health, CCJ Medical Devices, QinFlow, Hemostatics, Zibrio and Oxyband, He receives research grant support from the DoD, DARPA, NIH and CSL focused on hemorrhage control and resuscitation. He consults with BARDA, WFIRM, and Aspen Medical, is the co-inventor of the Junctional Emergency Tourniquet Tool and receive royalties from UT Health. The authors received no financial or in-kind support for this work.

#### **REFERENCES**

- James SL, Castle CD, Dingels ZV, Fox JT, Hamilton EB, Liu Z, et al. Global injury morbidity and mortality from 1990 to 2017: results from the Global Burden of Disease Study 2017. *Inj Prev.* 2020;26(Suppl 2):i96–i114.
- Holcomb JB, Jenkins D, Rhee P, Johannigman J, Mahoney P, Mehta S, et al. Damage control resuscitation: directly addressing the early coagulopathy of trauma. J Trauma Acute Care Surg. 2007;62(2):307–310.
- Borgman MA, Spinella PC, Perkins JG, Grathwohl KW, Repine T, Beekley AC, Sebesta J, Jenkins D, Wade CE, Holcomb JB. The ratio of blood products transfused affects mortality in patients receiving massive transfusions at a combat support hospital. *J Trauma*. 2007;63(4):805–813.
- Cannon JW, Khan MA, Raja AS, Cohen MJ, Como JJ, Cotton BA, et al. Damage control resuscitation in patients with severe traumatic hemorrhage: a practice management guideline from the Eastern Association for the Surgery of Trauma. *J Trauma Acute Care Surg.* 2017;82(3):605–617.
- Carmichael SP 2nd, Lin N, Evangelista ME, Holcomb JB. The story of blood for shock resuscitation: how the pendulum swings. *J Am Coll Surg.* 2021; 233(5):644–653.
- Blundell J. Experiments on the transfusion of blood by the syringe. Med Chir Trans. 1818;9(Pt 1):56–92.
- Kuhns WJ. Historical milestones blood transfusion in the civil war. *Transfusion*. 1965;5(1):92–94.
- Robertson OH. Transfusion with preserved red blood cells. Br Med J. 1918; 1(2999):691–695.
- Stansbury LG, Hess JR. Blood transfusion in World War I: the roles of Lawrence Bruce Robertson and Oswald Hope Robertson in the "most important medical advance of the war". *Transfus Med Rev.* 2009;23(3):232–236.
- Robertson LB. Further observations on the results of blood transfusion in war surgery: with special reference to the results in primary hemorrhage. Ann Surg. 1918;67(1):1–13.
- Beecher HK. Preparation of battle casualties for surgery. Ann Surg. 1945; 121(6):769–792.
- Black JA, Pierce VS, Kerby JD, Holcomb JB. The evolution of blood transfusion in the trauma patient: whole blood has come full circle. *Semin Thromb Hemost*. 2020;46(2):215–220.
- Miller RD, Robbins TO, Tong MJ, Barton SL. Coagulation defects associated with massive blood transfusions. Ann Surg. 1971;174(5):794–801.
- Shires GT, Canizaro PC. Fluid resuscitation in the severely injured. Surg Clin North Am. 1973;53(6):1341–1366.
- Henry S. ATLS 10th edition offers new insights into managing trauma patients. Bull Am Coll Surg. 2018.
- Cotton BA, Guy JS, Morris JA Jr., Abumrad NN. The cellular, metabolic, and systemic consequences of aggressive fluid resuscitation strategies. Shock. 2006;26(2):115–121.
- Barak M, Rudin M, Vofsi O, Droyan A, Katz Y. Fluid administration during abdominal surgery influences on coagulation in the postoperative period. *Curr Surg.* 2004;61(5):459–462.
- Eddy VA, Morris JA Jr., Cullinane DC. Hypothermia, coagulopathy, and acidosis. Surg Clin North Am. 2000;80(3):845–854.
- Weykamp MB, Stern K, Brakenridge SC, Robinson BR, Wade CE, Fox EE, Holcomb JB, O'Keefe GE. Prehospital crystalloid resuscitation: practice variation and associations with clinical outcomes. *Shock*. 2023;59(1):28–33.
- Robinson BRH, Cohen MJ, Holcomb JB, Pritts TA, Gomaa D, Fox EE, Branson RD, Callcut RA, Cotton BA, Schreiber MA, Brasel KJ, Pittet JF, Inaba K, Kerby JD, Scalea TM, Wade CE, Bulger EM, PROPPR Study Group. Risk factors for the development of acute respiratory distress syndrome following hemorrhage. Shock. 2018;50(3):258–264.

- Rotondo MF, Schwab CW, McGonigal MD, Phillips GR 3rd, Fruchterman TM, Kauder DR, et al. 'Damage control': an approach for improved survival in exsanguinating penetrating abdominal injury. *J Trauma*. 1993;35(3): 375–382.
- Holcomb JB, Wade CE, Michalek JE, Chisholm GB, Zarzabal LA, Schreiber MA, et al. Increased plasma and platelet to red blood cell ratios improves outcome in 466 massively transfused civilian trauma patients. *Ann Surg.* 2008; 248(3):447–458.
- 23. Holcomb JB, Del Junco DJ, Fox EE, Wade CE, Cohen MJ, Schreiber MA, 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):127–136.
- 24. Holcomb JB, Tilley BC, Baraniuk S, Fox EE, Wade CE, Podbielski JM, 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):471–482.
- Cotton BA, Reddy N, Hatch QM, LeFebvre E, Wade CE, Kozar RA, 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.
- 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 Acute Care Surg*. 2009;66(4):S69–S76.
- Kauvar DS, Holcomb JB, Norris GC, Hess JR. Fresh whole blood transfusion: a controversial military practice. J Trauma Acute Care Surg. 2006;61(1):181–184.
- Naumann DN, Boulton AJ, Sandhu A, Campbell K, Charlton W, Gurney JM, et al. Fresh whole blood from walking blood banks for patients with traumatic hemorrhagic shock: a systematic review and meta-analysis. *J Trauma Acute Care Surg*. 2020;89(4):792–800.
- 29. Gurney JM, Staudt AM, Del Junco DJ, Shackelford SA, Mann-Salinas EA, Cap AP, et al. Whole blood at the tip of the spear: a retrospective cohort analysis of warm fresh whole blood resuscitation versus component therapy in severely injured combat casualties. *Surgery*. 2022;171(2):518–525.
- Butler FK Jr., Holcomb JB, Schreiber MA, Kotwal RS, Jenkins DA, Champion HR, et al. Fluid resuscitation for hemorrhagic shock in tactical combat casualty care: TCCC guidelines change 14-01–2 June 2014. *J Spec Oper Med*. 2014 Fall;14(3):13–38.
- Shackelford SA, Gurney JM, Taylor AL, Keenan S, Corley JB, Cunningham CW, et al, Joint Trauma System Defense Committee on Trauma; Armed Services Blood Program. Joint Trauma System, Defense Committee on Trauma, and Armed Services Blood Program consensus statement on whole blood. *Transfusion*. 2021;61(Suppl 1):S333–S335.
- Cap AP, Beckett A, Benov A, Borgman M, Chen J, Corley JB, et al. Whole blood transfusion. *Mil Med.* 2018;183(suppl\_2):44–51.
- Holcomb JB, Spinella PC, Apelseth TO, Butler FK, Cannon JW, Cap AP, et al. Civilian walking blood bank emergency preparedness plan. *Transfusion*. 2021;61(Suppl 1):S313–S325.
- Yazer MH, Jackson B, Sperry JL, Alarcon L, Triulzi DJ, Murdock AD. Initial safety and feasibility of cold-stored uncrossmatched whole blood transfusion in civilian trauma patients. *J Trauma Acute Care Surg*. 2016;81(1):21–26.
- 35. Spinella PC, Cap AP. Whole blood: back to the future. *Curr Opin Hematol*. 2016;23(6):536–542.
- Hazelton JP, Ssentongo AE, Oh JS, Ssentongo P, Seamon MJ, Byrne JP, et al.
   Use of cold-stored whole blood is associated with improved mortality in hemostatic resuscitation of major bleeding: a multicenter study. *Ann Surg.* 2022;276(4):579–588.
- Shackelford SA, Del Junco DJ, Powell-Dunford N, Mazuchowski EL, Howard JT, Kotwal RS, et al. Association of prehospital blood product transfusion during medical evacuation of combat casualties in Afghanistan with acute and 30-day survival. *JAMA*. 2017;318(16):1581–1591.
- Fisher AD, Miles EA, Broussard MA, Corley JB, Knight R, Remley MA, et al. Low titer group O whole blood resuscitation: military experience from the point of injury. J Trauma Acute Care Surg. 2020;89(4):834–841.
- O'Reilly DJ, Morrison JJ, Jansen JO, Apodaca AN, Rasmussen TE, Midwinter MJ. Prehospital blood transfusion in the en route management of severe combat trauma: a matched cohort study. *J Trauma Acute Care Surg.* 2014;77(3): S114–S120.
- Sperry JL, Guyette FX, Brown JB, Yazer MH, Triulzi DJ, Early-Young BJ, et al. Prehospital plasma during air medical transport in trauma patients at risk for hemorrhagic shock. N Engl J Med. 2018;379(4):315–326.

- Guyette FX, Sperry JL, Peitzman AB, Billiar TR, Daley BJ, Miller RS, et al. Prehospital blood product and crystalloid resuscitation in the severely injured patient: a secondary analysis of the prehospital air medical plasma trial. *Ann* Surg. 2021;273(2):358–364.
- Moore HB, Moore EE, Chapman MP, McVaney K, Bryskiewicz G, Blechar R, et al. Plasma-first resuscitation to treat haemorrhagic shock during emergency ground transportation in an urban area: a randomised trial. *Lancet*. 2018;392(10144):283–291.
- Crombie N, Doughty HA, Bishop JR, Desai A, Dixon EF, Hancox JM, et al. Resuscitation with blood products in patients with trauma-related haemorrhagic shock receiving prehospital care (RePHILL): a multicentre, open-label, randomised, controlled, phase 3 trial. *Lancet Haematol*. 2022;9(4):e250–e261.
- Hashmi ZG, Jansen JO, Kerby JD, Holcomb JB. Nationwide estimates of the need for prehospital blood products after injury. *Transfusion*. 2022;62(Suppl 1): S203–S210.
- Yazer MH, Spinella PC, Bank EA, Cannon JW, Dunbar NM, Holcomb JB, et al. THOR-AABB working party recommendations for a prehospital blood product transfusion program. *Prehosp Emerg Care*. 2022;26(6):863–875.
- Braverman MA, Smith A, Pokorny D, Axtman B, Shahan CP, Barry L, et al. Prehospital whole blood reduces early mortality in patients with hemorrhagic shock. *Transfusion*. 2021;61(Suppl 1):S15–S21.
- Guyette FX, Zenati M, Triulzi DJ, Yazer MH, Skroczky H, Early BJ, et al. Prehospital low titer group O whole blood is feasible and safe: results of a prospective randomized pilot trial. *J Trauma Acute Care Surg.* 2022;92(5): 839–847.
- Cox ED, Schreiber MA, McManus J, Wade CE, Holcomb JB. New hemostatic agents in the combat setting. *Transfusion*. 2009;49(Suppl 5):248S–255S.
- Zietlow JM, Zietlow SP, Morris DS, Berns KS, Jenkins DH. Prehospital use of hemostatic bandages and tourniquets: translation from military experience to implementation in civilian trauma care. *J Spec Oper Med.* 2015 Summer; 15(2):48–53.
- Kragh JF Jr., Walters TJ, Baer DG, Fox CJ, Wade CE, Salinas J, Holcomb JB. Survival with emergency tourniquet use to stop bleeding in major limb trauma. *Ann Surg.* 2009;249(1):1–7.
- Hashmi ZG, Hu PJ, Jansen JO, Butler FK, Kerby JD, Holcomb JB. Characteristics and outcomes of prehospital tourniquet use for trauma in the United States. *Prehosp Emerg Care*. 2023;27(1):31–37.
- Howard JT, Kotwal RS, Stern CA, Janak JC, Mazuchowski EL, Butler FK, et al. Use of combat casualty care data to assess the US military trauma system during the Afghanistan and Iraq conflicts, 2001–2017. *JAMA Surg*. 2019;154(7):600–608.
- Vasudeva M, Mathew JK, Groombridge C, Tee JW, Johnny CS, Maini A, et al. Hypocalcemia in trauma patients: a systematic review. *J Trauma Acute Care Surg*. 2021;90(2):396–402.
- Voller J, Tobin JM, Cap AP, Cunningham CW, Denoyer M, Drew B, et al. Joint trauma system clinical practice guideline (JTS CPG): prehospital blood transfusion. 30 October 2020. J Spec Oper Med. 2021;21(4):11–21.
- Moore HB, Moore EE, Gonzalez E, Chapman MP, Chin TL, Silliman CC, et al. Hyperfibrinolysis, physiologic fibrinolysis, and fibrinolysis shutdown: the spectrum of postinjury fibrinolysis and relevance to antifibrinolytic therapy. *J Trauma Acute Care Surg.* 2014;77(6):811–817.
- Schöchl H, Frietsch T, Pavelka M, Jámbor C. Hyperfibrinolysis after major trauma: differential diagnosis of lysis patterns and prognostic value of thrombelastometry. J Trauma Acute Care Surg. 2009;67(1):125–131.
- 57. CRASH-2 trial collaborators, , Shakur H, Roberts I, Bautista R, Caballero J, Coats T, Dewan Y, et al. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. *Lancet*. 2010; 376(9734):23–32.
- 58. Morrison JJ, Dubose JJ, Rasmussen TE, Midwinter MJ. Military application of tranexamic acid in trauma emergency resuscitation (MATTERs) study. *Arch Surg*. 2012;147(2):113–119.
- Rowell SE, Meier EN, McKnight B, Kannas D, May S, Sheehan K, et al. Effect of out-of-hospital tranexamic acid vs placebo on 6-month functional neurologic outcomes in patients with moderate or severe traumatic brain injury. *JAMA*. 2020;324(10):961–974.
- Drew B, Auten JD, Cap AP, Deaton TG, Donham B, Dorlac WC, et al. The use of tranexamic acid in tactical combat casualty care: TCCC proposed change 20-02. J Spec Oper Med. 2020 Fall;20(3):36–43.
- Rourke C, Curry N, Khan S, Taylor R, Raza I, Davenport R, et al. Fibrinogen levels during trauma hemorrhage, response to replacement therapy, and association with patient outcomes. *J Thromb Haemost*. 2012;10(7):1342–1351.

- McQuilten ZK, Wood EM, Bailey M, Cameron PA, Cooper DJ. Fibrinogen is an independent predictor of mortality in major trauma patients: a five-year statewide cohort study. *Injury*. 2017;48(5):1074–1081.
- Holcomb JB, Fox EE, Zhang X, White N, Wade CE, Cotton BA, et al. Cryoprecipitate use in the prospective observational multicenter major trauma transfusion study (PROMMTT). J Trauma Acute Care Surg. 2013;75(1 Suppl 1): S31–S39.
- Winearls J, Campbell D, Hurn C, Furyk J, Ryan G, Trout M, et al. Fibrinogen in traumatic haemorrhage: a narrative review. *Injury*. 2017;48(2):230–242.
- Spahn DR, Bouillon B, Cerny V, Duranteau J, Filipescu D, Hunt BJ, et al. The European guideline on management of major bleeding and coagulopathy following trauma. *Crit Care*. 2019;23:1–74.
- 66. Innerhofer P, Fries D, Mittermayr M, Innerhofer N, von Langen D, Hell T, et al. Reversal of trauma-induced coagulopathy using first-line coagulation factor concentrates or fresh frozen plasma (RETIC): a single-centre, parallel-group, open-label, randomised trial. *Lancet Haematol*. 2017;4(6): e258–e271.
- Zeeshan M, Hamidi M, Feinstein AJ, Gries L, Jehan F, Sakran J, et al. Fourfactor prothrombin complex concentrate is associated with improved survival in trauma-related hemorrhage: a nationwide propensity-matched analysis. *J Trauma Acute Care Surg.* 2019;87(2):274–281.
- 68. Bouzat P, Charbit J, Abback PS, Huet-Garrigue D, Delhaye N, Leone M, et al. Efficacy and safety of Early administration of 4-factor prothrombin complex concentrate in patients with trauma at risk of massive transfusion: the PROCOAG randomized clinical trial. *JAMA*. 2023;329(16):1367–1375.
- 69. Sims CA, Holena D, Kim P, Pascual J, Smith B, Martin N, et al. Effect of low-dose supplementation of arginine vasopressin on need for blood product transfusions in patients with trauma and hemorrhagic shock: a randomized clinical trial. *JAMA Surg.* 2019;154(11):994–1003.
- Chang R, Kerby JD, Kalkwarf KJ, Van Belle G, Fox EE, Cotton BA, et al, PROPPR study group. Earlier time to hemostasis is associated with decreased mortality and rate of complications: results from the pragmatic randomized optimal platelet and plasma ratio trial. *J Trauma Acute Care Surg*. 2019;87(2):342–349.
- Holcomb JB. Transport time and Preoperating room hemostatic interventions are important: improving outcomes after severe truncal injury. *Crit Care Med*. 2018;46(3):447–453.
- Qasim Z, Butler FK, Holcomb JB, Kotora JG, Eastridge BJ, Brohi K, et al. Selective prehospital advanced resuscitative care—developing a strategy to prevent prehospital deaths from noncompressible torso hemorrhage. *Shock*. 2021;57(1):7–14.
- Rokayak OA, Lammers DT, Baird EW, Holcomb JB, Jansen JO, Cox DB, et al. The 16-year evolution of a military-civilian partnership: the University of Alabama at Birmingham experience. *J Trauma Acute Care Surg*. 2023.
- 74. Uhlich R, Hu P, Yazer M, Jansen JO, Patrician P, Marques MB, Reynolds L, Fifolt M, Stephens SW, Gelbard RB, Kerby J, Holcomb JB. The females have spoken: a patient-centered national survey on the administration of emergent transfusions with the potential for future fetal harm. *J Trauma Acute Care Surg*. 2023;94(6):791–797.
- Yazer MH, Panko G, Holcomb JB, Kaplan A, Leeper C, Seheult JN, Triulzi DJ, Spinella PC. Not as "D" eadly as once thought - the risk of D-alloimmunization and hemolytic disease of the fetus and newborn following RhD-positive transfusion in trauma. *Hematology*. 2023;28(1):2161215.
- Gelbard RB, Griffin RL, Reynolds L, Abraham P, Warner J, Hu P, Kerby JD, Uhlich R, Marques MB, Jansen JO, Holcomb JB. Over-transfusion with blood for suspected hemorrhagic shock is not associated with worse clinical outcomes. *Transfusion*. 2022;62(Suppl 1):S177–S184.
- Wu F, Chipman A, Pati S, Miyasawa B, Corash L, Kozar RA. Resuscitative strategies to modulate the endotheliopathy of trauma: from cell to patient. *Shock*. 2020;53(5):575–584.
- Kalkwarf KJ, Drake SA, Yang Y, Thetford C, Myers L, Brock M, et al. Bleeding to death in a big city: an analysis of all trauma deaths from hemorrhage in a metropolitan area during 1 year. *J Trauma Acute Care Surg.* 2020; 89(4):716–722
- Costantini TW, Galante JM, Braverman MA, Phuong J, Price MA, Cuschieri J, Godat LN, Holcomb JB, Coimbra R, Bulger EM, NTRAP acute resuscitation panel. Developing a National Trauma Research Action Plan: results from the acute resuscitation, initial patient evaluation, imaging, and management research gap Delphi survey. J Trauma Acute Care Surg. 2022;93(2): 200–208.