



## REVIEW

## Resuscitation and transfusion principles for traumatic hemorrhagic shock

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## SUMMARY

The transfusion approach to massive hemorrhage has continually evolved since it began in the early 1900s. It started with fresh whole blood and currently consists of virtually exclusive use of component and crystalloid therapy. Recent US military experience has reinvigorated the debate on what the most optimal transfusion strategy is for patients with traumatic hemorrhagic shock. In this review we discuss recently described mechanisms that contribute to traumatic coagulopathy, which include increased anti-coagulation factors and hyperfibrinolysis. We also describe the concept of damage control resuscitation (DCR), an early and aggressive prevention and treatment of hemorrhagic shock for patients with severe life-threatening traumatic injuries. The central tenants of DCR include hypotensive resuscitation, rapid surgical control, prevention and treatment of acidosis, hypothermia, and hypocalcemia, avoidance of hemodilution, and hemostatic resuscitation with transfusion of red blood cells, plasma, and platelets in a 1:1:1 unit ratio and the appropriate use of coagulation factors such as rFVIIa and fibrinogen-containing products (fibrinogen concentrates, cryoprecipitate). Fresh whole blood is also part of DCR in locations where it is available. Additional concepts to DCR since its original description that can be considered are the preferential use of “fresh” RBCs, and when available thromboelastography to direct blood product and hemostatic adjunct (anti-fibrinolytics and coagulation factor) administration. Lastly we discuss the importance of an established massive transfusion protocol to rapidly employ DCR and hemostatic resuscitation principles. While the majority of recent trauma transfusion papers are supportive of these general concepts, there is no Level 1 or 2 data available. Taken together, the preponderance of data suggests that these concepts may significantly decrease mortality in massively transfused trauma patients.

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## Introduction

Traumatic injury is the leading cause of death for patients between the ages of 1 and 40,<sup>1</sup> and approximately 90,000 people die per year in the US from traumatic injuries.<sup>2</sup> US military reports estimate that 15–20% of traumatic deaths are potentially preventable and 66–80% of these deaths occur from hemorrhage.<sup>3,4</sup> Rural civilian data indicate that approximately 10% of traumatic deaths are preventable,<sup>5,6</sup> and 16% of preventable deaths are due to hemorrhage.<sup>7</sup> If 10–20% of 90,000 US civilian traumatic deaths are preventable and 16–80% of these preventable deaths are due to uncontrolled bleeding this translates to between 1400 and 14,000 potentially preventable hemorrhagic trauma deaths per year in

the US. Hemorrhagic deaths typically occur very early, usually within the first 6 h of admission.<sup>8–11</sup> Early hypoperfusion or shock has been demonstrated to promote coagulopathy.<sup>12,13</sup> Approximately 25% of patients with severe traumatic injury are coagulopathic upon admission.<sup>14,15</sup> Shock and coagulopathy upon admission have been both independently associated with massive transfusion and increased mortality.<sup>16–19</sup> Therefore, early identification of patients who are at risk of developing shock and coagulopathy, and subsequent strategies to prevent and control these processes may improve survival.<sup>13,16,17,20,21</sup>

The transfusion approach to hemorrhage has continually changed since the early 1900s. This evolution has included fresh whole blood and modified whole blood to the current virtually exclusive use of component therapy and crystalloid with whole blood being reserved for uncommon indications.<sup>22–25</sup> After the development of whole blood fractionation, component therapy now predominates as the primary transfusion approach secondary to concerns for resource utilization and safety.<sup>25–27</sup> This change occurred without evidence documenting equivalent clinical outcome data between

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whole blood and component therapy.<sup>25–27</sup> In addition, regulatory approval of new storage solutions is based on RBC membrane viability and ATP concentrations instead of the ability of RBCs to deliver oxygen to the microvasculature or adverse effects on inflammation or immune function with stored RBCs.<sup>28</sup> Current transfusion guidelines regarding indications for blood components were based upon expert opinion, experiments in euvoletic patients requiring elective surgery and data from the modified whole blood era which is no longer commonly available.<sup>25–27</sup> With new storage solutions, the age of transfused RBCs has progressively increased over time to a current limit of 42 days, without prospective studies evaluating the clinical effect of increased RBC storage length on critically ill patients.<sup>22,28</sup>

Prompted by new data from combat casualties, an evolution of opinion is occurring in the trauma and transfusion medicine communities regarding the optimal resuscitative approach to hemorrhagic shock.<sup>27,29,30</sup> Damage control resuscitation (DCR) is the overall guiding concept to emerge from the recent military experience.<sup>29–32</sup> DCR which includes permissive hypotension as first described by Cannon in 1918 can be summarized as allowing the blood pressure to be slightly less than normal to promote thrombus formation while still providing enough perfusion to end organs.<sup>33</sup> In other words, the goal of permissive hypotension is to prevent increasing the blood pressure to a threshold where a forming thrombus will not be able to achieve hemostasis, and re-bleeding occurs. This has been called “popping the clot”.<sup>34</sup> This concept is practiced prior to surgical control. The practice and literature supporting permissive hypotension have been well documented and will not be discussed further.<sup>32–36</sup> DCR also advocates for the rapid control of surgical bleeding, prevention of acidosis, hypocalcemia and hypothermia, and for the limitation of excessive crystalloid use to decrease hemodilution. All of these principles are intended to prevent inducing or exacerbating a hypocoagulable state in these patients with severe traumatic injury who are at high risk of developing severe shock and coagulopathy. Hemostatic resuscitation is also a component of DCR and is a term to describe a unified transfusion approach to severe hemorrhagic shock.<sup>31,37,38</sup> Hemostatic resuscitation advocates for the transfusion of RBCs, plasma, and platelets in a 1:1:1 ratio and for the use of thawed plasma to achieve this ratio upon admission. This approach is also intended to minimize exacerbating a dilutional coagulopathy by replacing lost blood with plasma and platelet-containing products instead of early and large amounts of crystalloids and RBCs. Hemostatic resuscitation is also theoretically intended to address the consumptive coagulopathy and perhaps improve endothelial function which is currently being evaluated in multiple in vitro experiments. Adjuncts to hemostatic resuscitation include the appropriate use of coagulation factor and fibrinogen-containing products.<sup>39–43</sup> Fresh whole blood is also part of DCR in locations where it is available. Additional concepts that can be considered as a part of DCR include the preference for fresh RBCs,<sup>19,44–47</sup> and the potential use of thromboelastography to fine tune empiric blood product transfusion ratios and to direct the administration of coagulation factor products, and anti-fibrinolytics.<sup>24,48</sup>

The literature supporting these changes advocated by DCR has been met with appropriate caution and skepticism.<sup>49</sup> A proposed change of practice should always be done carefully and thoughtfully and in a data-driven fashion, it is important to recognize that the literature supporting the current ATLS standard for the past 25 years was based upon 18 patients.<sup>50</sup>

While most of the literature reviewed is in patients with traumatic injury, further study is appropriate in different patient populations, such as those massively bleeding from ruptured aortic aneurysms,<sup>51</sup> gastrointestinal or obstetric sources to determine if DCR concepts apply in these circumstances.

## Traumatic coagulopathy and acute coagulopathy of trauma-shock

Traumatic coagulopathy is a hypocoagulable state that occurs in the most severely injured.<sup>14,15,52,53</sup> There are multiple factors that may contribute to this coagulopathy, which evolve over time. Immediately after injury, hypoperfusion may cause coagulopathy as a result of increased anti-coagulation and hyperfibrinolysis via increased activated protein C production, tissue plasminogen activator and a concomitant decrease in plasminogen activator inhibitor concentrations and thrombin activatable fibrinolysis inhibitor.<sup>13,24</sup> This specific process has been termed the Acute Coagulopathy of Trauma-Shock (ACoTS).<sup>12</sup> Mathematical models have determined that hemodilution occurs after patients are given excessive crystalloids and red blood cells (RBCs) worsening shock-induced hypocoagulation.<sup>26,54</sup> The development of hypothermia, hypocalcemia and acidosis can each further contribute to worsening of this initial coagulopathic state.<sup>24</sup> The degree of hypocoagulation upon admission has been determined to be independently associated with massive transfusion and mortality in trauma patients.<sup>14,15,17,20</sup> Since death from hemorrhage occurs quickly, usually within 6 h from injury,<sup>9,55,56</sup> the rapid identification of coagulopathy and its treatment may improve survival. This is the central tenant of DCR. Recent adult military and civilian retrospective studies support this concept.<sup>18,37,57–64</sup> Severely injured trauma patients frequently present with traumatic coagulopathy and ACoTS with significant bleeding as a result of injury and hypocoagulation.<sup>14,15,52</sup> Over time this process can shift or progress to DIC, especially when associated with sepsis. It is very important to recognize that Traumatic coagulopathy and ACoTS are different from Disseminated Intravascular Coagulation (DIC). Traumatic coagulopathy is a hypocoagulable state that is multi-factorial as described above. Patients who survive their early hypocoagulable state can progress to DIC which is a hypercoagulable state, possibly due to release of thromboplastins or diffuse endothelial injury secondary to inflammation.<sup>65</sup> Differentiating between these two distinct processes is difficult since both present similarly with active bleeding. Unfortunately, standard coagulation testing (PT/PTT, fibrinogen and platelet counts) cannot easily differentiate between these two disorders accurately. One method that may differentiate between traumatic coagulopathy and DIC (hypo and hypercoagulable states) is thromboelastography (TEG).<sup>66</sup> The differentiation between these two processes is important since the optimal treatments are different.

## DCR concepts and tools

Damage control resuscitation and hemostatic resuscitation are concepts that have been recently developed to describe what is currently thought by many to be the optimal resuscitative and transfusion approach to patients with hemorrhagic shock and immediately life-threatening injuries.<sup>29–32</sup> Similar to damage control surgery the goal of damage control resuscitation is to “stay out of trouble instead of getting out of trouble”. Therefore in patients with severe traumatic injury the goal is to minimize iatrogenic resuscitation injury, prevent worsening of the presenting traumatic shock and coagulopathy, and to obtain definitive hemostasis. Once this is achieved the next immediate goal is to rapidly reverse shock, hypocoagulation, intravascular volume depletion, and maintain appropriate oxygen delivery and cardiac output. Fortunately, these measures are required infrequently as massive transfusion patients comprise only 3–8% of civilian and military trauma admissions, respectively.<sup>57,60,67</sup> DCR concepts and tools are listed in Table 1.

**Table 1**  
Damage control resuscitation principles.

Rapid recognition of high risk for trauma-induced coagulopathy (massive transfusion prediction)
Permissive hypotension
Rapid definitive/surgical control of bleeding
Prevention/treatment of hypothermia, acidosis, and hypocalcemia
Avoidance of hemodilution by minimizing use of crystalloids
Early transfusion of red blood cells:plasma:platelets in a 1:1:1 unit ratio
Use of thawed plasma and fresh whole blood when available
Appropriate use of coagulation factor products (rFVIIa) and fibrinogen-containing products (fibrinogen concentrates, cryoprecipitate)
*Use of fresh RBCs (storage age of <14 days)
*When available thromboelastography to direct blood product and the hemostatic adjunct (anti-fibrinolytics and coagulation factor) administration

Abbreviations: RBCs, red blood cells; rFVIIa, recombinant activated factor VII.  
\* Added components of DCR since original description that can be considered.

*Rapid recognition of risk for trauma-induced coagulopathy (Prediction of Massive Transfusion)*

Patients who develop traumatic coagulopathy often require a Massive Transfusion (MT) defined as 10 or more units of RBCs within the first 24 h of admission in adults.<sup>16</sup> Prediction of a MT is one of our most critical tasks for future research since mortality is high (Table 2) and rapid implementation of the appropriate MT guideline seems to improve survival.<sup>68</sup> Likewise, those not predicted to require a MT could avoid unnecessary exposure to blood products. Prediction tools for MT in adult trauma patients have been developed for both military and civilian trauma patients with predominantly penetrating and blunt injuries, respectively, with specificities that range between 80% and 90%.<sup>16,17,69,70</sup> These prediction equations typically include blood pressure, heart rate, base

**Table 2**  
Summary of plasma:RBC ratio in massive transfusion populations.

Author	Design	Single or multicenter	Number of MT patients	Predominant mechanism of injury	Inclusion criteria	Exclusion criteria	Time ratio measured	Main results	Mortality (%) low to high ratio groups	Significant limitations
Borgman MA <sup>57</sup>	R	Multi*	246	Penetrating	≥ 10 RBC in 24 h	Transfer from another facility	24 h	+ (adj)	65–34–19	Did not exclude early deaths subject to survivorship bias
Maegele M <sup>59</sup>	RPCD	Multi	713	Blunt	≥ 10 RBC in 24 h	Death in ED	ED and OR (3–6 h)	+ (adj)	46–36–30	No adj for confounding variables with mortality
Holcomb JB <sup>58</sup>	R	Multi	466	Mixed	≥ 10 RBC in 24 h	Death < 30 min from admission	24 h	+	67–27	No adj for confounding variables with mortality
Sperry JL <sup>63</sup>	RPCD	Multi	415	Blunt	≥ 8 RBC in 12 h	Penetrating injury	12 h	+ (adj)	35–28	Did not exclude early deaths subject to survivorship bias
Gunter OL <sup>37</sup>	R	Single	259	Mixed	≥ 10 RBC in 24 h	Death in ED <sup>§</sup>	24 h	+ (adj)	62–41	Did not include measures of acidosis and coagulopathy in regression analysis
Duchesne JC <sup>38</sup>	R	Single	135	Mixed	≥ 10 RBC in 24 h	Death in ED	24 h	+ (adj)	88–26	Did not include measures of acidosis and coagulopathy in regression analysis
Zink KA <sup>61</sup>	R	Multi	452	Mixed	≥ 10 RBC in 24 h	Death < 30 min from admission	6 h	+ (adj)	55–41–25	No adj for confounding variables with mortality
Kashuk JL <sup>98</sup>	R	Single	133	Mixed	≥ 10 RBC in 6 h	Severe TBI as cause of death	6 h	+ (adj)	77–37–55	Underpowered
						ER thoracotomy		For ≥ 1:2		11 patients in high ratio group
						Chronic medical conditions		– (adj)		5 years study
Scalea TM <sup>99</sup>	P	Single	81	Not reported for MT patients	≥ 10 RBC in 24 h	Death in ED or OR	24 h	– (adj)	14 (all patients)	Underpowered
								For 1:1 FFP:RBC		Did not include measures of acidosis and coagulopathy in regression analysis
								– (adj)		Excluding OR deaths may remove patients who die from not enough plasma
Snyder CW <sup>95</sup>	R	Single	134	Mixed	≥ 10 RBC in 24 h	None	24 h	+ – (adj)	35–28%	Underpowered
										Number of variables per outcome in regression above recommended
Teixeira PG <sup>97</sup>	R	Single	383	Not reported	≥ 10 RBC in 24 h	Severe TBI	24 h	+ (adj)	90–49–25–26%	Did not include measures of acidosis and coagulopathy or platelet and factor VIIa use in regression analysis
								For ≥ 1:3 FFP:RBC		Six year study

+ Indicates high plasma:RBC ratio was associated with survival.  
– Indicates high plasma:RBC ratio was not associated with survival.

If study reported for patients with and without massive transfusion as defined by authors only information and results for massive transfusion population reported.

Abbreviations: Multi, multicenter; MT, massive transfusion; RBC, red blood cell units; ED, Emergency Department; OR, operating room; adj, adjusted results with logistic regression; TBI, traumatic brain injury; R, retrospective; P, prospective; RPCD, retrospective with prospectively collected data.

\* Indicates one US Military facility that had multiple groups of physicians rotate through it with multiple style and practice differences.

§ Exclusion of patients who died in the ED was not published but was confirmed by authors.

deficit, INR, and hemoglobin values, and Focused Assessment with Sonography in Trauma (FAST) examination. The primary advantage of using these prediction models is that they augment the ability to immediately determine upon admission which patients will require a DCR strategy. At times it is obvious that patients with severe injuries and profound hypotension will need a massive transfusion, but patients with significant internal bleeding who may be in a state of compensated shock it may not be clear. It is in this patient population that rapidly applicable prediction tools maybe most valuable. The quicker the hemorrhagic shock and quicker the need for massive transfusion can be recognized, the quicker it can be appropriately addressed. Cotton et al. evaluated this principle by developing a multidisciplinary massive transfusion guideline and a comprehensive performance improvement assessment and have documented an association with increased survival with earlier application of a predefined MT guideline.<sup>68</sup> They evaluated all MT patients during two time periods, 2004–2006 and 2006–2008. In 2006 an agreed upon transfusion guideline was implemented and outcomes were compared to those of the preceding two years. The blood products were transfused in a ratio of 3:2 RBC:plasma units and 5:1 RBC:apheresis platelet units (1 apheresis platelet unit is equal to 5–6 random donor platelet units). The latter group had a lower MOF rate 20% vs. 9%,  $p < 0.01$ , and a higher 30-day survival 38% vs. 57%,  $p < 0.01$ . The differences were attributed to rapid and earlier transfusion of increased plasma and platelets ratios. Cotton and colleagues have also described a predictive score for MT with similar sensitivity and specificity to other predictive models for MT that does not require laboratory evaluation, it includes; penetrating mechanism, positive focused assessment sonography for trauma, arrival systolic blood pressure of 90 mm Hg or less, and arrival heart rate  $\geq 120$  bpm.<sup>70</sup>

The TASH score developed by Yucel et al. was from the Trauma Registry of the German Trauma Society.<sup>69</sup> It is a prospective multicenter database with standardized documentation of patients with severe trauma requiring ICU care. This registry comprises detailed information on demographics, clinical and laboratory data, as well as a variety of standardized scoring systems on injury severity, e.g. the Glasgow Coma Score, the Injury Severity Score (ISS), the Abbreviated Injury Scale (AIS), and the Trauma and Injury Severity Score. From 1993 to 2003, a total of 17,200 patients from 100 participating hospitals in Germany ( $n = 90$ ), Austria ( $n = 8$ ), The Netherlands ( $n = 1$ ), and Switzerland ( $n = 1$ ) were included on a voluntary basis.<sup>69</sup> The TASH score was developed from 4527 patients and then validated in 1517 patients. The score ranging from 0 to 28 is based upon physiologic and laboratory data and can be determined within the first 15 min of admission. It was determined to have an area under the curve of 0.89 in both the development and validation data sets.<sup>69</sup> A TASH score of 16 correlates to a 50% prediction of MT. Studies are underway to determine if predictive models such as the TASH score can be used to determine which patients upon admission can be rapidly identified as requiring hemostatic resuscitation.

### Thromboelastography

Thromboelastography is a laboratory method that may facilitate targeted or goal directed hemostatic resuscitation. It is a rapid point-of-care test that qualitatively measures the entire coagulation cascade, including fibrinolysis, in whole blood. Compared to thromboelastography, the standard approach of measuring the coagulation system in patients has several disadvantages. It usually takes longer to get PT/PTT, INR, platelet and fibrinogen concentrations results (30–60 min) than initial thromboelastography parameters (10 min). Although with the recent development of point-of-care INR and PT measurement the timing of these results is less of a

concern. Prothrombin time and PTT only evaluate partial aspects of the coagulation cascade, and since these standard tests are performed with plasma, the interaction between coagulation factors and platelets cannot be assessed. In addition, fibrinogen and platelet function cannot be measured rapidly with standard testing as is possible with thromboelastography. Platelet concentration may not always equate with platelet function which is accurately measured by TEG to include the anti-platelet effect of platelet inhibitors. When compared to standard coagulation testing thromboelastography appears to be more accurate at detecting multiple aspects of coagulopathy and possibly for predicting blood product requirements.<sup>52,71–75</sup> Since thromboelastography is the only method that can measure fibrinolysis it can determine which patients would potentially benefit from the use of an anti-fibrinolytic. An additional advantage of thromboelastography is that it may be able to guide appropriate use of rFVIIa and may provide more accurate measurements of rFVIIa efficacy than PT.<sup>48,76,77</sup> Recent data also suggest that thromboelastography can identify hypercoagulable states days after admission and can identify patients at risk for thrombotic events, even when these patients are receiving deep vein thrombosis prophylaxis and have therapeutic concentrations of anti-factor Xa.<sup>78,79</sup> Future studies are needed to correlate TEG results with current transfusion practices and outcomes, to evaluate the potential role of thromboelastography and to direct blood product administration, coagulation factor replacement, and anti-fibrinolytics for patients with hemorrhagic shock in addition to monitoring of anti-coagulation.

### Avoidance of hemodilution

The current standard approach taught in the Advanced Trauma Life Support (ATLS) course for adults with significant bleeding is to initially administer 1–2 l of isotonic crystalloids and then to transfuse RBCs until coagulopathy is recognized by laboratory analysis at which point plasma should be transfused. In addition, practice guidelines for blood component therapy by the American Society of Anesthesiologists Task Force on Blood Component Therapy suggest that platelet transfusion is indicated for surgical patients with microvascular bleeding when the serum platelet concentration is less than 50,000–100,000.<sup>80</sup> This approach is appropriate for the roughly 92–97% of trauma patients who are not significantly hypovolemic, in shock and who do not require a massive transfusion.<sup>30</sup> For the 3–8% of trauma patients who require a massive transfusion this approach frequently results in liters of RBC and crystalloid transfusion, exacerbating their coagulopathy and increasing their risk of death from hemorrhage. Multiple studies have indicated that approximately 25–30% of adult trauma patients present to the emergency room in a coagulopathic state and this early coagulopathy is highly correlated with mortality.<sup>14,15,20,53</sup> Adverse clinical outcomes associated with over-resuscitating critically ill patients with crystalloids were described by FD Moore and Shires G in 1968,<sup>81</sup> were reiterated in a recent review by Cotton,<sup>82</sup> and were confirmed in prospective cohort studies<sup>83</sup> and randomized-controlled trials.<sup>84,85</sup> In addition to the hemodiluting effects of excessive crystalloids for patients at high risk of coagulopathy, the pro-inflammatory nature of crystalloids is under-appreciated and is also well described in Cotton's review.<sup>82</sup> The same concerns exist for the over use of RBCs in the initial phase of the resuscitation of a patient in hemorrhagic shock. When large amounts of RBCs are initially transfused this further hemodilutes the patient, secondary to plasma protein dilution, and may also contribute to exacerbating a hyper-inflammatory and immune deficient state, especially when older RBCs are transfused.<sup>86–90</sup> To minimize the development of a dilutional coagulopathy, DCR principles advocate for the minimal use of crystalloids and the use of plasma, RBCs, and

platelets in a 1:1:1 ratio for patients at high risk of death secondary to hemorrhage from traumatic injuries.

#### Plasma, RBCs, platelets in a 1:1:1 ratio and fresh whole blood

Until very recently there has been very little literature to guide the use of blood components in the resuscitation of patients with hemorrhagic shock. In fact the only randomized-controlled trial examining the efficacy of platelets compared to that of plasma was performed by Reed et al. in 33 patients with massive transfusion.<sup>91</sup> The concept of transfusing plasma, RBCs, and platelets in a 1:1:1 ratio results from the philosophy that if you are bleeding massive amounts of whole blood you should be replacing whole blood to prevent a rapid death from hemorrhage in patients with severe traumatic injury. Data from US Military casualties indicate that survival is increased for patients who receive warm fresh whole blood compared to those who receive only component therapy.<sup>19</sup> Since fresh or even whole blood is no longer available at most institutions, practitioners have had to adjust to the availability of components only and transfuse plasma, RBCs, and platelets in a 1:1:1 ratio (reconstituted whole blood). In the past 12 years after the transition from whole blood to components, many studies have suggested that increased plasma and platelets were required for patients with severe traumatic injury and hemorrhage.<sup>26,54,92–94</sup> In 1997, Cosgrif et al. reported on a cohort of 58 massively transfused non-head injury trauma patients to determine risk factors for developing life-threatening coagulopathy. A comparison of blood product usage in those who survived vs. those who died demonstrated platelets/PRBC unit transfusion ratio of 0.79 vs. 0.48 ( $p = 0.01$ ).<sup>92</sup> Then in 1999 Cinat et al. reported for patients with massive transfusion an increased ratio of plasma:RBC and platelets:RBC was associated with improved survival.<sup>94</sup>

Currently there are 13 large adult US Military and civilian retrospective studies, both single and multicenter, in penetrating and blunt injury massive transfusion populations, which mostly indicate that when groups of equal severity of injury are compared, a high ratio of plasma and platelets to RBCs, (approximating a median 1:1:1 unit ratio) is associated with improved survival (Tables 2 and 3). A few of these studies have documented that this survival benefit was associated with decreased death from hemorrhage.<sup>57,58,60</sup> Additionally, there is a prospective cohort study that indicates that patients with severe bleeding secondary to ruptured aortic aneurysms have improved survival with a 1:1 ratio of plasma to RBCs and increased platelet transfusion.<sup>51</sup> Since the majority of these reports are retrospective and subject to bias, particularly survivorship bias, they must be interpreted with caution. Survivorship bias in this situation means that plasma and platelets were available only for those patients who were bleeding slowly enough

to receive them, and that rapidly bleeding patients died before receiving the products. It is important to note though that many of these studies have excluded patients who died within the first 30–60 min or in the emergency department, specifically to minimize this concern.<sup>37,38,58–61,64</sup> This exclusion period should have removed those patients who were bleeding to death within the time when plasma and platelets were unavailable. Even with excluding these patients, an association between increased ratios of plasma and platelets to RBCs with increased survival still remains.<sup>37,38,58–61,64</sup> It is unclear if the increased death in patients receiving low plasma and platelet to RBC ratios is due to a delay in treating coagulopathy or to a true survival bias in these retrospective studies. A report by Snyder et al. concluded that after adjustment for survival bias a high ratio of plasma:RBCs was not independently associated with survival.<sup>95</sup> While future analyses require a time-dependent approach to adjust for survivorship bias the analysis by Snyder et al. is significantly limited by a lack of statistical power due to their small sample size of 134 patients. In addition, their multivariate regression analysis is limited by using 9–12 variables in a study of 134 patients with 67 outcomes of interest. In this study there were 7.4–5.6 variables per outcome of interest which is well below the standard of at least 10 variables per outcome.<sup>96</sup> The omission of determining if collinearity existed in the 9–12 variables may have also decreased the accuracy of their survivorship bias analysis.

Another criticism of the studies supporting high ratios of plasma and platelets to RBCs is that the use of 24-h ratios may not reflect the need to transfuse increased amounts of plasma and platelets early in the resuscitation. The concern is ratios could be low initially and then upon survival in the ICU “catch up” transfusion of plasma and platelets occurs. To address this concern the use of 6- and 12-h ratios has been performed in civilian databases and again the relationship between increased ratios of plasma and platelets with RBCs to increased survival remains and is actually stronger than that measured with 24-h ratios.<sup>59,61,63</sup> Additional limitations within some of these studies are the lack of logistic regression analysis to adjust for confounders with mortality<sup>58,61</sup> and when performed some regression analyses did not include measures of shock and coagulopathy.<sup>97–99</sup> Conversely, two studies have been published which question if a 1:1:1 ratio of components is the optimal approach for massive transfusion patients.<sup>98,99</sup> When analyzing these studies it is important to evaluate the severity of injury of patients included, sample size and which patients are excluded. Both of these studies are underpowered when patients with massive transfusion are considered.<sup>98,99</sup> The study by Kashuk et al. included only 11 patients in the high plasma:RBC ratio group, and was performed over a 5-year time period.<sup>98</sup> In addition limitations of the report by Scalea et al.<sup>99</sup> include the exclusion

**Table 3**  
Summary of platelet:RBC ratio studies in massive transfusion patients.

Author	Design	Single or multicenter	Number of patients	Predominant mechanism of injury	Inclusion criteria	Exclusion criteria	Time ratio measured	Main results	Mortality (%) low to high ratio groups	Significant limitations
Holcomb JB <sup>58</sup>	R	Multi	466	Mixed	≥ 10 RBC in 24 h	Death < 30 min from admission	24 h	+	67–27	No adj for confounding variables with mortality Combat casualties Generalizability for civilian casualties No adj for confounding variables with mortality Retrospective, limited data on actual timing of transfusions
Perkins JG <sup>60</sup>	R	Multi*	462	Penetrating	≥ 10 RBC in 24 h	Death < 60 min from admission	24 h	+ (adj)	57–40–25	
Zink KA <sup>61</sup>	R	Multi	452	Mixed	≥ 10 RBC in 24 h	Death < 30 min from admission	6 h	+	44–47–27	
Holcomb JB <sup>64</sup>	R	Multi	643	Mixed	≥ 10 RBC in 24 h	Death < 60 min from admission	24 h	+ (adj)	46–38–24	

+ Indicates high platelet:RBC ratio was associated with survival.

Abbreviations: Multi, multicenter; RBC, red blood cell units; adj, adjusted results with logistic regression.

\* Indicates one US Military facility that had multiple groups of physicians rotate through it with multiple style and practice differences.

of patients who died in the operating room (OR), not being able to adjust for measures of shock or coagulopathy which is required for a thorough logistic regression analysis and most importantly including patients not requiring massive transfusion. Since the risk of death from hemorrhage for patients transfused less plasma and platelets is highest within the first 6 h of admission,<sup>57,60</sup> the exclusion of patients who died in the OR excludes patients who would have potentially benefited from increased plasma or platelet transfusion. In other words, this sampling bias excludes analyzing patients at highest risk of mortality who were transfused lower ratios of plasma and platelets to RBCs. While the report by Scalea et al. included 806 patients, only 81 patients with massive transfusion were analyzed.<sup>99</sup> Based upon inclusion and exclusion criteria the transfused patients in this manuscript had a low mortality of 14%<sup>99</sup> compared to the 35–70% mortality for patient populations in the studies that support the use of a high (1:1) plasma to RBC ratio.<sup>37,38,57–61,63</sup> The preponderance of the current literature indicates that patients in hemorrhagic shock at high risk of death or who require massive transfusion benefit from increased ratios of plasma and platelets to RBCs. Conversely, DCR should not be performed in patients who are not in hemorrhagic shock or who are not at high risk of massive transfusion. **Tables 2 and 3** summarize all of the recent studies on outcomes related to plasma:RBC and platelet:RBC ratios in patients with traumatic injuries requiring massive transfusion. The American Association of Blood Banks (AABB) has performed an evidenced-based review for the AABB plasma guideline project and has concluded that massive transfusion appears to be one situation where giving plasma prevents death and multi-organ failure despite increases in acute lung injury.<sup>100</sup>

The risks of plasma and platelet use must be considered with increased use. Plasma transfusion has been associated with increased risk of allergic reactions, transfusion-associated acute lung injury (TRALI), transfusion-associated cardiac overload (TACO), and acute respiratory distress syndrome (ARDS).<sup>101</sup> Platelet transfusion has been associated with each of these in addition to bacterial contamination, deep venous thromboembolism (DVT), and febrile reactions.<sup>101</sup> The risks of these adverse events have not been well quantified with a wide range of reported occurrences. The reported incidence of TRALI ranges from 1/500 to 1/5000 to 1/60,000 for platelets, all blood components, and fresh frozen plasma transfusion, respectively.<sup>102,103</sup> Lack of recognition and underreporting very likely contributes to these results. In patients without severe bleeding these risks, even though they are uncommon, likely outweigh their potential benefit. For patients with severe traumatic injury and hemorrhagic shock the apparent survival benefit with increased plasma and platelet transfusion far exceeds the uncommon to rare risks of transfusion reactions, TRALI, TACO, and infections that can be associated with their use. What should also be recognized is that the standard of predominantly transfusing RBCs for patients with hemorrhagic shock also increases the risk of infection, ARDS, DVT, multi-organ failure and even death with increased RBC use.<sup>44,90,104,105</sup> An increased risk of death with increased use of RBCs as a secondary outcome has been reported in a large prospective randomized-controlled trial (TRICC Trial) where critically ill patients who received just a few more units of RBCs had increased in-hospital mortality.<sup>106</sup> So while the risks of plasma and platelet use should always be acknowledged, these risks should be placed in perspective with the potential benefits of improved survival when increased amounts are transfused early to patients with severe traumatic hemorrhage. Just as importantly, the risks of increased plasma and platelet use should also be put in perspective with the increased risk of multi-organ failure and death associated with the increased transfusion of RBCs in critically ill patients.<sup>18,90,104,105,107,108</sup>

Fresh whole blood has been defined in multiple ways in the literature. It has been defined as either whole blood at room temperature for less than 24 h or refrigerated at 4 °C for less than 48 h.<sup>109</sup> When a 1:1:1 unit ratio of each blood component is desired for resuscitation the most efficient product to use is fresh whole blood.<sup>109</sup> When compared to a unit of whole blood that is reconstituted with one unit each of RBCs, plasma, and platelets, one unit of fresh whole blood is a more concentrated and functional product.<sup>110</sup> Fresh whole blood is logistically very difficult to supply in most civilian settings in the developed world, although with the appropriate infrastructure and planning it can be made available as it is in both remote locations and urban areas with high trauma rates.<sup>109</sup> A recent report indicated that in patients with severe traumatic injury the use of fresh whole blood was independently associated with improved survival when compared to patients transfused component therapy with similar severity of injury.<sup>19</sup> While 2 prospective randomized-controlled trials in post-op pediatric cardiac surgery populations have indicated improved outcomes with the use of fresh whole blood compared to component therapy,<sup>111,112</sup> there have been no prospective trials in patients with traumatic injury. Level 1 evidence is needed to support the increased logistical support that would be required to make fresh whole blood available in large trauma centers.

#### *Thawed plasma*

Thawed plasma is fresh frozen plasma that is brought to 1–6 °C and stored for up to 5 days. This timeline was based on preservation of factor V and VIII levels and similar to RBC storage solutions there are no clinical outcomes data associated with this time period. Typically type AB plasma is used for emergent use of thawed plasma since it is the universal donor type for plasma. While use of thawed plasma has been routine in several large trauma centers, many more have recently added this capability in their Emergency Departments (EDs). This immediate availability of both RBCs and plasma allows for the initiation of transfusion of these products in a 1:1 ratio upon admission for patients identified as being at high risk for massive transfusion. Vigilant inventory management of thawed plasma in trauma centers with high volume significantly (albeit anecdotally) reduces the risk of plasma waste as a result of this practice. The availability of thawed plasma is essential for the rapid initiation application of a 1:1:1 transfusion strategy. This strategy is very difficult to achieve when plasma is to be thawed upon arrival. Studies documenting improved resource utilization and outcomes with the use of thawed plasma compared to frozen plasma products are needed. A recent study indicates that thawed plasma, stored at 4 °C, retains significant clotting function for up to 14 days and meets AABB standards; however, there are no clinical outcome data associated with this approach.<sup>113</sup> Research on outcomes associated with thawed plasma stored for this duration and what percent of coagulation function is required for patients in hemorrhagic shock also needs to be explored.

#### *Fresh RBCs*

RBCs can be stored for 42 days with current FDA-approved solutions. Over time changes occur to stored red cells that are potentially harmful.<sup>44,104,105</sup> This has been termed the storage lesion. The storage age in which RBCs start to have significant adverse effects ranges from greater than 5–7 days in relation to hyperkalemia to greater than 14–28 days regarding hyper-inflammatory, immune dysfunction, impaired vasoregulation and perfusion concerns.<sup>44,86,90,104,105,107,108</sup> Despite a considerable amount of adverse effects in laboratory, animal, and large well-conducted retrospective human studies, there is in general a reluctance to limit the use of older RBCs in critically ill patient populations who are at

the highest risk of adverse effects from their transfusion.<sup>28</sup> The transfusion of old (>14–28 days) RBCs has been independently associated with increased risk of infection, multi-organ failure, and death in critically ill adult populations (sepsis and trauma) in retrospective studies.<sup>45,46,114,115</sup> There is also evidence that old RBCs may increase the risk of deep vein thrombosis and mortality in adults with traumatic injury.<sup>47</sup> Preliminary evidence from a planned secondary analysis in a large prospective study of transfused critically ill children also indicates that the use of RBCs >14 days of storage, after adjustment for severity of illness and RBC amount, increases the risk of multi-organ failure.<sup>116</sup>

The understandable reluctance to limit the use of old RBCs in critically ill patients is in part due to the lack of well-designed prospective randomized-controlled studies and the concern of increased waste of RBCs from the preferential use of young RBCs in some patients.<sup>28</sup> It is also likely true that the older RBCs are not harmful and potentially efficacious in non-critically ill patients who only receive a few RBC units. While these concerns are valid it is also important to realize that RBCs greater than 14 days of storage in current approved storage solutions have never been documented to improve oxygen consumption for patients in a shock state. In fact there is evidence to the contrary. In laboratory experiments and animal models older RBCs do not increase oxygen consumption or perfusion while fresh RBCs can.<sup>117–120</sup> So, while there is not prospective randomized evidence that old RBCs increase mortality, there is also no evidence that old RBCs are functional in critically ill patients and the preponderance of the evidence indicates that they are potentially harmful especially in severely injured patients who are already in a hyper-inflammatory, immuno-modulatory state with impaired vasoregulation.<sup>90,107,108</sup> It is for these reasons that some advocate for the use of fresh ( $\leq$ 14–21 days) RBCs for massively transfused patients<sup>44,90</sup> and others express concern with the use of older RBCs in this population.<sup>104,105,107,108</sup> In recognition of these data, the US Department of Defense has recently modified their blood inventory system, decreasing the age of transfused blood in critically injured combat casualties. Two large prospective randomized-controlled trials will start soon in adults to attempt to answer this question in a general critically ill population and in post-operative cardiac surgery adult patients. A clinical trial specifically in patients with severe traumatic injury and hemorrhagic shock is clearly needed.

## Adjuncts to hemostatic resuscitation

### *Alkaline and calcium therapy*

While it appears to be important to prevent acidosis and hypocalcemia there is no evidence to support that the reversal of acidosis and hypocalcemia improve outcomes. In fact there are some studies that indicate when acidosis is treated coagulopathy is not reversed.<sup>121</sup> While these practices are controversial and definitive studies have not been performed it is not unusual for alkaline solutions such as sodium bicarbonate or THAM (tromethamine) to be given to reverse acidosis and calcium solutions to treat hypocalcemia which commonly occurs with massive transfusion.

### *Recombinant factor VIIa*

Another controversial subject is the use of rFVIIa for patients with severe traumatic injuries. While two randomized prospective trials in adult trauma have indicated decreased use of RBCs for patients treated with rFVIIa and in one a decreased rate of ARDS<sup>42</sup> there are no prospective data to support improved survival as a result of its use in this circumstance. Recently a large multi-national phase III trial of rFVIIa in trauma patients was terminated due to

futility with a much lower expected mortality than planned. One retrospective study of adult US Military trauma patients has reported increased 30-day survival for patients with severe traumatic injury and massive transfusion, but this was a small study of just over 100 patients and multivariate logistic regression was not performed to determine an independent association between the use of rFVIIa and survival.<sup>43</sup> What was intriguing in this study was the hypothesis that early use of rFVIIa (median 2 h from admission or 2.5 h from injury) was a factor in the improved survival in this report compared to other studies where rFVIIa was used later in the hospital course. The conundrum of what patient population may benefit and how to determine this continues to be controversial. Perhaps additional studies which utilize TEG can help determine which patients would potentially benefit from the use of rFVIIa.<sup>48</sup> Despite all of the concerns of severe thrombotic events with rFVIIa use there have been multiple prospective RCTs in surgical patients who have been performed with rFVIIa and none have reported an increased incidence or adverse events.<sup>43</sup> This has also been reported in a recent Cochrane review of the topic.<sup>122</sup> Few drugs (and no blood products) commonly used in trauma patients have undergone such a rigorous evaluation and shown such strong safety results.

### *Fibrinogen*

Whether the liberal use of cryoprecipitate (or in Europe fibrinogen concentrates) for patients requiring massive transfusion improves survival is also controversial. Animal studies indicate that fibrinogen decreases early in trauma models due to hyperfibrinolysis and other studies in thrombocytopenic animal models report that fibrinogen improves coagulopathy better than platelet transfusion.<sup>39,40,123,124</sup> In addition, a recent US Military retrospective review also determined that patient's transfused increased amounts of fibrinogen had better outcomes as a result of decreased death from hemorrhage<sup>41</sup> and another larger study of combat casualties with massive transfusion indicates that the amount of cryoprecipitate transfused within the first 24 h, after adjusting for severity of illness, was independently associated with improved 30-day survival.<sup>60</sup> The standard of transfusing fibrinogen-containing solutions only after the fibrinogen concentration is less than 100 mg/dl has not been studied in patients with traumatic injury and appears to be based more upon expert opinion than upon data. Additional study is needed to determine what concentrations of fibrinogen are appropriate in this population. The use of TEG, which can indirectly assess fibrinogen function and directly measure hyperfibrinolysis, also needs to be studied to determine if it can be used to determine indications for the use of fibrinogen-containing solutions and most importantly improve outcomes.

## Massive transfusion protocols

A recent survey has been reported on the use of massive transfusion protocols (MTPs) world-wide in adult patients.<sup>24</sup> In this survey it is self-reported that 45% of respondents use a MTP, 19% use one sporadically, and 34% do not. The development of a massive transfusion protocol for patients with severe life-threatening bleeding is important to standardize the approach to these patients and to provide structure and organization to what is usually a chaotic situation.<sup>125</sup> Important aspects of a MTP are standardization of the assessment of coagulopathy and the ratio of blood products empirically delivered. In addition a MTP should also call attention to the assessment and treatment of acidosis, hypothermia and hypocalcemia. Cotton et al. have studied the clinical affect of implementing a standardized MTP compared to historical controls and have documented improved survival and decreased organ

failure.<sup>68,126</sup> In another recent study by Dente, for patients with blunt traumatic injury, the use of a massive transfusion protocol that prescribed the use of RBCs, plasma, and platelets in a 1:1:1 unit ratio was associated with increased plasma and decreased crystalloid use in the first 24 h, improved 24 h and 30-day survival, and decreased early death from hemorrhage when compared to historical control patients of similar injury.<sup>127</sup>

## Conclusion

Trauma is the most common cause of death for patients 1–40 years of age, death from hemorrhagic shock is the most common cause of preventable death within 6 h of admission, and the rapid identification and treatment of coagulopathy may improve survival. Therefore, it is imperative that we understand the pathophysiology of traumatic coagulopathy and ACoTS better, and develop methods to decrease death from hemorrhage. We must also continue to develop research protocols to determine the optimal transfusion approach for patients with traumatic shock. In addition, other conditions with severe bleeding and hemorrhagic shock such as aortic aneurysm rupture, post-operative cardiac surgery, gastrointestinal and obstetric bleeding require similar attention. Current data indicate that the early identification of coagulopathy and its treatment with RBCs, plasma, and platelets in a 1:1:1 unit ratio achieved with the use of fresh RBCs, thawed plasma, and platelets, limited use of crystalloids, and possibly with the early and appropriate use of rFVIIa and cryoprecipitate may improve survival in uncommon patient who presents with severe traumatic injury and life-threatening bleeding. In addition, rapid surgical control of the source of bleeding with prevention or treatment of acidosis, hypothermia and hypocalcemia is essential. Lastly, the use of thromboelastography-directed anti-fibrinolytics for hyperfibrinolysis is promising and requires prospective study. These principles of DCR should only be applied for patients with life-threatening bleeding with hemorrhagic shock and should not be over used or mis-applied. Accurate predictive models that can be performed upon admission may be able to identify the patients who will benefit from hemostatic resuscitation. These models must be prospectively validated and should be a high priority of future research since they will allow for the appropriate indication and exclusion of hemostatic resuscitation principles. All blood products including RBCs, plasma and platelets have adverse effects and each should only be used when absolutely necessary. The US Department of Defense has funded a prospective observational transfusion trial at 10 busy trauma centers, and these data will start to answer many of the questions raised in this review. Future prospective randomized studies are required to definitively answer what approach best balances benefit and risk.

## Conflict of interest statement

No conflict of interest.

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