

# Damage Control Resuscitation: The New Face of Damage Control

*Juan C. Duchesne, MD, FACS, FCCP, Norman E. McSwain, Jr., MD, FACS, Bryan A. Cotton, MD, FACS, John P. Hunt, MD, MPH, FACS, Jeff Dellavolpe, MD, Kelly Lafaro, MD, MPH, Alan B. Marr, MD, FACS, Earnest A. Gonzalez, MD, FACS, Herb A. Phelan, MD, FACS, Tracy Bilski, MD, FACS, Patrick Greiffenstein, MD, James M. Barbeau, MD, JD, Kelly V. Rennie, MD, Christopher C. Baker, MD, FACS, Karim Brohi, MD, FRCS, FRCA, Donald H. Jenkins, MD, FACS, and Michael Rotondo, MD, FACS*

Damage control resuscitation has become a topic of increasing relevance and popularity over the past several years. Hemorrhage accounts for 30% to 40% of trauma fatalities and is the leading cause of preventable death in trauma.<sup>1</sup> Damage control resuscitation (DCR) is a treatment strategy that targets the conditions that exacerbate hemorrhage in trauma patients. New data from both civilian medical centers and military operations in the Iraq and Afghanistan conflicts have allowed for a reappraisal of the resuscitation techniques of the trauma victim. The emergence of the idea of DCR has fostered controversy regarding its overall efficacy, its associated mortality, and the scientific basis of such a strategy. This article attempts to answer some of the overarching questions associated with the acute care and resuscitation of the trauma patient. Topics reviewed and discussed will include DCR and surgery, transfusion ratios, permissive hypotension, recombinant factor VIIa (rFVIIa), hypertonic fluid solutions, and the destructive forces of hypothermia, acidosis, and coagulopathy. We will also investigate some of the implications of DCR as they pertain to the future of resuscitation and the optimization of trauma care in the future.

Originally coined by the US Navy in reference to techniques for salvaging a ship, which had sustained serious damage,<sup>2</sup> the term “damage control” has been adapted to truncating initial surgical procedures on severely injured patients to provide only interventions necessary to control hemorrhage and contamination to focus on reestablishing a survivable physiologic status.

These temporized patients would then undergo continued resuscitation and aggressive correction of their coagulopathy, hypothermia, and acidosis in the intensive care unit (ICU) before returning to the operating room (OR) for the definitive repair of their injuries. This approach has been shown to lead to better-than-expected survival rates for abdominal trauma,<sup>3–10</sup> and its application has now been extended to include thoracic surgery<sup>3</sup> and early fracture care.<sup>4–8</sup>

Discussions of damage control surgery usually center on the type and timing of surgical procedures. Recently, methods of resuscitation of patients with exsanguinating hemorrhage have come under increasing scrutiny for their ability to adequately correct the acidosis, hypothermia, and coagulopathy seen in these patients.<sup>9,10</sup> DCR is a concept that has been popularized by the military and is now being studied in the civilian setting. DCR differs from current resuscitation approaches by attempting an earlier and more aggressive correction of coagulopathy and metabolic derangement. The concept centers around the assumption that coagulopathy is actually present very early after injury, and earlier interventions to correct it in the most severely injured patients may lead to improved outcomes. DCR centers on the application of several key concepts, namely, the permissive hypotension, the use of blood products over isotonic fluid for volume replacement, and the rapid and early correction of coagulopathy with component therapy.<sup>11</sup> This resuscitation strategy begins from ground zero in the emergency room (ER) and continues through the OR and into the ICU.

Understanding the physiologic sequelae of exsanguinating hemorrhage and the complex interaction of hypothermia, acidosis, and coagulopathy is central to an appreciation for the potential benefits of DCR.<sup>12</sup> In addition, as with any new therapy, there exists some controversy with regard to its efficacy, impact on outcomes, and the scientific evidence behind the strategy. This review will examine the basis and state of DCR, address some of the controversy of this strategy of resuscitation and its relationship to damage control surgery, and suggest its role in the future of resuscitation and the optimization of prognosis after trauma.

## PERMISSIVE HYPOTENSION

The concept behind permissive hypotension involves keeping the blood pressure low enough to avoid exsanguina-

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From the Tulane School of Medicine Health Science Center (J.C.D., N.E.M., J.D., K.L., K.V.R.), New Orleans, Los Angeles; University of Texas Health Science Center (B.A.C., E.A.G.), Houston, Texas; Louisiana State University Health Science Center (J.P.H., A.B.M., P.G., J.M.B., C.C.B.), New Orleans, Los Angeles; University of Texas Southwestern Medical Center (H.A.P.), Dallas, Texas; The University of Mississippi Medical Center (T.B.), Jackson, Mississippi; Royal London Hospital (K.B.), London, United Kingdom; Mayo Clinic (D.H.J.), Rochester, Minnesota; and The Brody School of Medicine at East Carolina University (M.R.), North Carolina.

Address for reprints: Juan C. Duchesne, MD, FACS, FCCP, Section of Trauma and Critical Care Surgery, Department of Surgery and Anesthesia, Tulane University School of Medicine, 1430 Tulane Avenue, SL-22, New Orleans, LA 70112-2699; email: jduchesn@tulane.edu.

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tion while maintaining perfusion of end organs. Although hypotensive resuscitation is evolving into an integral part of the new strategy of DCR, the practice itself is not a new concept. Walter Cannon and John Fraser remarked on it as early as 1918 when serving with the Harvard Medical Unit in France during World War I. They made the following observations on patients undergoing fluid resuscitation: "Injection of a fluid that will increase blood pressure has dangers in itself. Hemorrhage in a case of shock may not have occurred to a marked degree because blood pressure has been too low and the flow too scant to overcome the obstacle offered by the clot. If the pressure is raised before the surgeon is ready to check any bleeding that may take place, blood that is sorely needed may be lost."<sup>13</sup> Dr. Cannon's endpoint of resuscitation before definitive hemorrhage control was a systolic pressure of 70 mm Hg to 80 mm Hg, using a crystalloid/colloid mixture as his fluid of choice.

In World War II, Beecher promulgated Cannon's hypotensive resuscitation principles in the care of casualties with truncal injuries. "When the patient must wait for a considerable period, elevation of his systolic blood pressure (SBP) to ~85 mm Hg is all that is necessary ... and when profuse internal bleeding is occurring, it is wasteful of time and blood to attempt to get a patient's blood pressure up to normal. One should consider himself lucky if a systolic pressure of 80 mm Hg to 85 mm Hg can be achieved and then surgery undertaken."<sup>14</sup>

Although these anecdotal reports from earlier generations of surgeons are interesting, more scientific attempts to examine outcomes for permissive hypotension after serious injury have been mixed. The most well-known study that displayed a benefit for delayed aggressive fluid resuscitation until after operative intervention with surgical hemostasis was published in 1994 by Bickell et al. This randomized controlled trial of patients with penetrating truncal injuries compared mortality rates of patients who received immediate versus delayed administration of intravenous (IV) fluids and discovered improved survival, fewer complications, and shorter hospital stays in the delayed group. They demonstrated that, regardless of the victim's blood pressure, survival was better in their urban "scoop and run" rapid transport system when no attempt at prehospital resuscitation was made.<sup>15</sup> The same group published a follow-up abstract in 1995, which was a subgroup analysis of the previous study dividing patients into groups by their injury type. This study demonstrated a lack of effect on survival, in most groups, for patients treated with delayed fluid resuscitation with a survival advantage only for patients with penetrating injuries to the heart ( $p = 0.046$ ).<sup>16</sup> This called into question whether study by Bickell et al. was generalizable to trauma population at large. Four years later, Burris et al.<sup>17</sup> also suggested that patients could benefit in the short-term by resuscitating to a lower blood pressure. Other studies attempting to replicate these results were unable to find a difference in survival.<sup>18,19</sup> Also of note is whether these results in a penetrating trauma population can be extrapolated to the trauma population at large remains to be seen.

In 2006, Hirshberg et al.<sup>20</sup> used computer modeling to demonstrate that the timing of resuscitation has different effects on bleeding, with an early bolus delaying hemostasis and increasing blood loss and a late bolus triggering rebleeding. Animal models exploring the effect of fluid administration on rebleeding have been equally contradictory, with some demonstrating that limiting fluids reduces hemorrhage,<sup>21</sup> whereas others demonstrate that fluids do not increase bleeding.<sup>22</sup> Moreover, the limited use of fluids during resuscitation efforts is in direct opposition to guidelines put forth by the American College of Surgeons and the Advanced Trauma Life Support protocol.<sup>23</sup>

The discussion about the risks and benefits of permissive hypotension beg additional questions: even if one believes that permissive hypotension is beneficial, it seems intuitive that some low threshold of safety should exist. How low of a blood pressure can the injured patients tolerate? For how long? Does this theoretical lower limit change when considering not only the initial hypotensive/hypoxic injury but reperfusion injury as well? At the other end of the spectrum, at what level of blood pressure do we "pop the clot" off of spontaneously clotted vessels? Does this point vary with types of resuscitation fluid, time of onset, rate of resuscitation, and the nature of the wound? How does permissive hypotension come into play in the setting of multiple injuries? Most of the work in this modality has been done in penetrating trauma. What is the role of permissive hypotension in blunt trauma? This is an especially pertinent question in injuries where hypotension has been shown to be detrimental, such as brain injury. This important point of contention that, in severe traumatic brain injury (TBI), denying fluids can attenuate the injury by decreasing the intracerebral perfusion pressure has been entertained before.<sup>24,25</sup>

Unfortunately, no evidence-based recommendations exist from any of the field's leading trauma organizations. In their absence, the findings from historical military medical sources, modern urban transport studies, and recent laboratory animal models suggest that trauma patients without definitive hemorrhage control should have a limited increase in blood pressure until definitive surgical control of bleeding can be achieved. The potential for rebleeding against the detrimental effects of systemic ischemia and reperfusion require further study. Until more detailed studies are conducted, hard guidelines cannot be put forth.

## ISOTONIC CRYSTALLOIDS

Resuscitation has long been used to refer to the medical treatment of lost fluid volume in one form or another. For modern deliverers of acute medical care, it means primarily one thing: isotonic saline solution. However, faced with the current studies in this field, it has become necessary to reconsider the popularly held notion that isotonic fluid administration in large boluses for acute hemorrhagic loss or severe traumatic injury requiring massive transfusion is the optimal therapy. Its place as the mainstay of initial therapy for the patient in hemorrhagic shock is predicated on the early work of Carrico and coworkers,<sup>26,27</sup> which revolves on observations of fluid and salt shifts in the intracellular and

extracellular spaces after hemorrhagic shock. Although isotonic and hypotonic saline solutions still have their place in the armamentarium of the trauma team, especially in patients who do not require large amounts of resuscitation fluid, the view of these as a panacea for hemodynamic instability in the subset of patients with massive exsanguination should be reexamined.

Also of importance in severe injury and shock is the incipient global state of ischemia. Oxygen-starved cells throughout the body enter a state of anaerobic metabolism with an overproduction of oxygen radicals and other toxic metabolites. Reestablishing effective circulation causes a steep increase in the levels of these toxic compounds, overwhelming the tissue free-radical scavengers and resulting in significant cellular injury.<sup>28</sup> This is worsened by the activation of inflammatory cells and the burst of inflammatory mediators, including cytotoxic compounds produced by activated neutrophils, which are in abundance in tissues highly susceptible to injury such as the lung, liver, and gastrointestinal (GI) tract. As a result, these organs are particularly sensitive to hypoxic insult and express this sensitivity in the form of acute respiratory distress syndrome (ARDS), systemic inflammatory response syndrome (SIRS), and multiple system organ failure (MSOF). It is also important to point out that, because this process has already commenced when the trauma patient arrives in shock, any intervention that will improve tissue perfusion (reverse shock) will produce some degree of tissue injury. Therefore, the question really becomes not which resuscitation strategy will be best but which will be least harmful. It is important to recognize that although isotonic fluid helps to decrease oxygen debt by improving flow and, hence, oxygen delivery at the cellular level, it does not increase oxygen carrying capacity or help correct the coagulopathy associated with severe hemorrhage.

Also of note, recent reports have also described potential mechanisms for the detrimental effects of early, aggressive crystalloid resuscitation as crystalloids have been found to have profound systemic and cellular complications.<sup>29</sup> Rhee et al.<sup>30</sup> have demonstrated that isotonic resuscitation can elicit severe immune activation and upregulation of cellular injury markers and worsen the acidosis and coagulopathy of trauma. These actions may in turn lead to an increased likelihood for developing the ARDS, SIRS, and MSOF.<sup>21</sup> Although not specific for trauma and conducted in the postresuscitative period, the Fluid and Catheter Treatment Trial, by the ARDSNET group, demonstrated significantly less vent days in a group of ventilated critically ill patients that were treated with less crystalloid.<sup>31</sup>

These observations have fostered the genesis of the strategy of minimal use of crystalloids and more reliance on the use of blood products, known as DCR.<sup>11</sup> Although resuscitation with crystalloids can initially improve blood pressure, there is strong evidence that fluids in and of themselves do nothing to help prevent the pathologic processes that coincide with severe trauma. One of the prime mechanisms by which crystalloids can contribute to poor outcome in severe trauma is the exacerbation of the components of the “death triad” of acidosis, hypothermia, and coagulopathy.

Crystalloids can cause a dilutional coagulopathy and do little for the oxygen carrying capacity needed to correct anaerobic metabolism and the oxygen debt associated with shock. The use of unwarmed fluids can also be implicated as a major cause for hypothermia. Also, because of its supraphysiologic concentration of chloride, crystalloids have been associated with hyperchloremic acidosis and the worsening of trauma patients existing acidosis.<sup>1</sup>

As a result of the pathologic changes associated with trauma, capillary permeability increases causing a loss of osmotic pressure and a loss of fluid to the interstitial and intracellular space.<sup>29</sup> Isotonic, hypotonic, and colloid solutions given postinjury have been shown to leak and cause edema with only a fraction remaining within the intravascular system. This fluid shift, magnified by conventional fluid resuscitation protocols, can have profound systemic consequences adding further insult to organs already compromised by the initial injury.

In the lungs, fluid extravasation and increased permeability of the pulmonary capillaries can lead to pulmonary edema and increased difficulty maintaining oxygen saturations.<sup>32</sup> In the GI tract, splanchnic edema can increase intra-abdominal pressure and cause a decrease in tissue oxygenation, increased gut susceptibility to infection, and impaired wound healing.<sup>33</sup> In the most extreme case, increased GI fluid sequestration can lead to abdominal compartment syndrome, a common complication of large volume crystalloid resuscitation in critically ill trauma patients.<sup>34</sup>

In addition to changes because of interstitial leakage of fluid and resultant tissue swelling, excessive administration of fluids can also cause imbalances at the cellular level, causing cellular swelling with resultant dilution of intracellular proteins and dysfunction of protein kinases, ultimately leading to decreased function of many cell types, including hepatocytes, pancreatic islet cells, and cardiac myocytes.<sup>29</sup>

The landmark study by Bickell et al. presented evidence that prehospital fluid administration was detrimental to survival when compared with patients subjected to “scoop and run” tactics where minimal to no fluids were administered before arrival in the hospital. In particular, the authors reported higher prothrombin time (PT)/partial thromboplastin time (PTT), longer hospital stays, and decreased survival associated with prehospital fluid administration suggesting that fluid-induced hemodilution may have played a significant part in the poor outcome in these patients.<sup>15</sup> Although limited in depth, the study revealed a need to reassess early resuscitation and how isotonic crystalloids were being used.

## HYPERTONIC SALINE

One interesting option for maintaining limited volume resuscitation is hypertonic saline (HTS), which has been a research focus for resuscitation efforts for several decades.<sup>35</sup> First explored in the 1980s and thought to be a viable resuscitation option, military researchers subsequently found HTS attractive for its ability to raise blood pressure quickly at much lower volumes of infusion than isotonic fluids and, thus, potentially easier to use and transport into combat. In numerous human, animal, and in vitro studies, HTS has been

found to exhibit a great many potentially beneficial effects on various aspects of the physiologic and immunologic response to injury that could have a tremendous impact on postresuscitation recovery from severe trauma.

Severe injury and hemorrhage induce fluid losses from the intravascular space that are compounded by the administration of IV resuscitation using hypo- or isotonic crystalloid solutions. In theory, the reason HTS has a more robust impact as a volume-restoring fluid is that it acts by increasing serum osmolarity, inducing a shift of fluid volume from the intracellular space into the extracellular space, and drawing volume into the intravascular system where it is most needed to maintain perfusion. Work by Mazzone et al.<sup>36</sup> showed that HTS resuscitation reversed the capillary endothelial swelling that occurs early on after hypotensive shock and thus not only improved systemic hemodynamics but also improved microcirculatory blood flow that was not amenable to conventional therapy of isotonic fluid resuscitation. In summary, HTS simultaneously allows for rapid restoration of circulating intravascular volume with less administered fluid and attenuates the postinjury edema at the microcirculatory level to possibly improve tissue perfusion.

HTS has also been shown to have profound immunomodulatory properties. Animal studies have been performed, which demonstrate the beneficial effects of HTS on attenuating the markers of injury and inflammation in both the lungs<sup>37</sup> and the gut.<sup>38</sup> Human studies by Rizoli et al. and Bulger et al., among others, have corroborated these findings. Rizoli et al. found that in hemorrhagic trauma patients, administration of HTS resulted in decreased neutrophil activation, reduced serum tumor necrosis factor  $\alpha$  levels, increased levels of the anti-inflammatory cytokines interleukin 1 $\alpha$  and interleukin 10, and attenuation of the shock-induced norepinephrine surge. Moreover, they also found that these effects lasted for over 24 hours, long after the transient rise in serum osmolarity had normalized.<sup>39</sup> Bulger et al. also found immune modulation in HTS-administered trauma patients, which supported preclinical studies by Rizoli et al. and Rotstein,<sup>40</sup> demonstrating that the anti-inflammatory effects were attributable to a transient inhibition of neutrophil CD11b expression.

### HTS in TBIs

Given the prevalence of head injury in the trauma population and the fact that it so often accounts for postinjury mortality (40–60% of postinjury mortality throughout the postinjury period),<sup>41</sup> it is necessary to address this issue in the development of resuscitation strategies. Several studies have found HTS to be a safe option in brain-injured trauma patients. Shackford et al.<sup>42</sup> found several desired effects as a result of the use of HTS, including a favorable fluid balance and control of intracranial pressure. Simma et al. also found HTS advantageous in the treatment of children with head injury and reported improved outcomes including fewer interventions necessary to keep intracranial pressure  $\leq 15$  mm Hg, shorter ICU stays, and fewer days of mechanical ventilation in comparison with the standard resuscitation. Furthermore, they noted systemic benefits to this treatment modality that resulted in fewer systemic complications including

ARDS, pneumonia, sepsis, and arrhythmias.<sup>43</sup> The effects of restored microvascular flow, decreased tissue edema, and attenuated inflammatory response have a particularly important role to play in patients with brain injury where cerebral edema can have profound irreversible effects when aggressive fluid resuscitation is needed to maintain global hemodynamics.<sup>44</sup>

### HTS in Clinical Practice

Several studies have been performed to determine the safety and efficacy of hyperosmotic solution in trauma resuscitations. Mattox et al. was the first in the United States to conduct a multicenter trial to compare HTS with dextran (HSD) with standard resuscitation. Their study demonstrated that HSD was safe, with lower incidence of ARDS, renal failure, and coagulopathy, but was not able to demonstrate a difference in overall survival because of insufficient sample size.<sup>45</sup> In 1997, Wade et al.<sup>46</sup> conducted a meta-analysis of controlled clinical studies that showed an increased survival of HSD over normal saline in seven of eight clinical trials. Although there are many benefits to be derived from HSD in trauma resuscitations, there are also certainly many risks and concerns associated with this type of treatment. A review by Dubick et al. in 2005 highlighted several of the issues of concern that might be seen with HSD. The first of these is the risk of uncontrolled bleeding, which can be seen with administration of any fluid that raises intravascular pressure. Hyperchloremic acidosis is seen in patients administered HTS because of its supraphysiologic concentration of chloride. Cellular dehydration is another concern involved with administering hypertonic fluids, especially in trauma patients. Neurologic deficits from transient hypernatremia, specifically central pontine myelinolysis (CPM), are a theoretical risk, which has not been borne out in the human trials. There is currently no evidence in the literature of the CPM seen in the rapid correction of hyponatremia in the setting of HTS administration.<sup>47</sup> CPM has not been reported in human trials using HTS for TBI. As such, most sources suggest keeping the serum sodium below 155 and not raising it greater than 10 mEq/d. Finally, the use of HSD in repeated doses was examined, and again, evidence suggests a great deal of tolerance based in large part on animal studies. The authors concluded that HSD administration, although not without some expected negative consequences, poses a minimal risk in comparison with other available treatment modalities.<sup>48</sup> Therefore, given the weight of favorable data, of which only a portion have been described here, the use of HTS as a potential tool in the resuscitation of severely traumatized individuals should be explored further and administration protocols developed that will exploit all of its beneficial effects in a safe, effective manner.

## COMPONENTS OF COAGULOPATHY

### Hypothermia

Hypothermia is common,<sup>49</sup> and severe hypothermia is associated with a high mortality.<sup>50</sup> Recent data from the 31st Combat Support Hospital in Iraq showed that 18% of casualties were hypothermic, with these patients all experiencing worse outcomes.<sup>51</sup> In general, prognosis is directly related to

the degree of hypothermia,<sup>52</sup> with a 100% mortality observed in patients who present with a core body temperature under 32.8°C, even when controlling for other comorbidities.<sup>53</sup> The actual causes of hypothermia are varied and range from the trauma itself to the various aspects of the resuscitation effort. After the initial insult of trauma, normal central thermoregulation is altered, and the shivering response is blocked. At the same time, the metabolic activity of tissues begins to slow, resulting in decreased heat production.<sup>52</sup> Evidence exists supporting the notion that most cases of hypothermia occur later in the resuscitation period after presentation to the ER.<sup>53,54</sup> During this initial evaluation and resuscitation, cold IV fluid has been implicated as the fastest way of accelerating hypothermia,<sup>2</sup> whereas the most common cause of heat loss is seen in the OR through the exposure of the peritoneum. Burch et al.<sup>55</sup> demonstrated that the average heat loss during laparotomy is 4.6°C per hour. In addition, Hirshberg et al.<sup>54</sup> demonstrated through graphic modeling that, during a damage control laparotomy, irreversible physiologic insult because of hypothermia resulted from cases lasting only 60 minutes to 90 minutes.

Hypothermia causes and exacerbates bleeding abnormalities through several mechanisms. First, low body temperature can affect platelet function both by decreasing the responsiveness of shear-induced platelet activation<sup>12</sup> and inducing reversible platelet sequestration in the liver and spleen.<sup>52</sup> In addition, enzyme activity is affected by low body temperatures, causing disturbances in enzyme kinetics (at 35°C, factors XI and XII are only functioning at 65% of normal).<sup>56</sup> Cold also alters fibrinolysis and decreases thromboxane B2 production.<sup>52</sup> The combined effects of temperature on these various components of the coagulation cascade can be very difficult to predict, as demonstrated by Watts et al.,<sup>57</sup> who showed that hypothermic patients were hypercoagulable with a body temperature >34.0°C but hypocoagulable with body temperatures <34.0°C.

The effects of hypothermia on coagulation occur through different and distinct mechanisms; thus, hypothermia-induced coagulopathy may be difficult to correct with normal resuscitation techniques. Animal studies have shown that hypothermia-induced changes in the coagulation system may be refractory to blood product administration and can only be reversed with rewarming.<sup>52,58,59</sup> Rewarming can be undertaken both passively and actively. Passive rewarming techniques such as covering the patient can be beneficial but also involves the expenditure of oxygen and could cause a further worsening of acidosis. Active rewarming techniques such as heating blankets, body cavity lavage, and warmed IV fluids are generally more invasive but ensure a quicker correction of the hypothermia of trauma.<sup>60</sup> Heating blankets using convection to transfer heat have been shown to increase core warming in patients from 1.4°C/h to 2.1°C/h.<sup>52</sup> However, in severely hypothermic patients, peripheral vasoconstriction may decrease the effectiveness of forced air warming. Body cavity lavage uses water instead of air used by the heating blankets, which has a 32 times greater rate of heat transfer and is generally performed in the peritoneum. Although it is a simple procedure, receiving adequate fluid return can be

difficult and is contraindicated in patients with hemoperitoneum, previous laparotomy, or free intra-abdominal air.<sup>52</sup> Warmed IV fluids increase the core body temperature via conduction and is more effective than heating blankets or body cavity lavage.<sup>52</sup> There are currently in line IV fluid warmers, which use dry heat, water baths, or counter current water baths. Counter current water baths potentially allow for the infusion of ~750 mL of crystalloids or 1 unit of blood per minute at eutermic temperatures.<sup>52</sup> New ideas in rewarming include continuous arteriovenous rewarming, which has been described as a method of rapidly correcting a cold core body temperature.<sup>61</sup> In this technique, percutaneously placed arterial and venous femoral catheters are connected to the inflow and outflow ports of a fluid warmer to use the patient's own arterial pressure to drive blood flow through the circuit and warm it extracorporeally. Its major limitation lies in the requirement of an adequate mean arterial pressure to drive flow. However, when able to be used, it has resulted in significantly faster rewarming times (39 minutes to correction of hypothermia vs. 3.2 hours in a control arm) and better outcomes.<sup>62</sup>

## Acidosis

Metabolic acidosis is the predominant physiologic defect resulting from persistent hypoperfusion,<sup>10</sup> and its systemic effects have a deleterious effect on an already compromised cardiovascular system. Acidosis at or below pH of 7.2 is associated with decreased contractility and cardiac output, vasodilation, hypotension, bradycardia, increased dysrhythmias, and decreased blood flow to the liver and kidneys.<sup>63</sup> Furthermore, acidosis can also act synergistically with hypothermia in its detrimental effect on the coagulation cascade. Meng et al. noted that pH strongly affected the activity of factor VIIa, reducing the enzyme's activity by 90% as the pH decreased from 7.4 to 7.0.<sup>64</sup> The pH also affects the PT through depression of factor X and factor V activity.<sup>56,64</sup> Cosgriff et al.<sup>65</sup> found that PT/PTT was more than twice normal in half of the patients with an Injury Severity Score (ISS) more than 25 and pH <7.1. Acidosis also has an inhibitory effect on thrombin generation rates, causing significant problems with hemostasis in the bleeding trauma victim.<sup>1</sup>

Many intrinsic causes of acidosis in trauma exist, including lactic acidosis, resuscitation with crystalloid fluid,<sup>1</sup> and the previously mentioned added effect of hypothermia. Shivering itself can cause a fourfold increase in oxygen consumption, whereas cold can cause a decrease in respirations and exacerbate hypoglycemia.<sup>52</sup> Moreover, the effects of both hypothermia and acidosis on thrombin generation and factor VII activity are additive in the trauma patient experiencing both conditions.<sup>12</sup> Hypothermia affects pH to such a degree that Watts et al.<sup>57</sup> were able to demonstrate that temperature causes six times more variability in acidosis than injury severity.

More sensitive measures of the adequacy of cellular oxygenation are the base deficit and serum lactate. The base deficit is a measure of the number of millimoles of base required to correct the pH of a liter of whole blood to 7.40, and its normal value is -3 to +3. This determination is readily available as it can be measured on a blood gas analysis, and

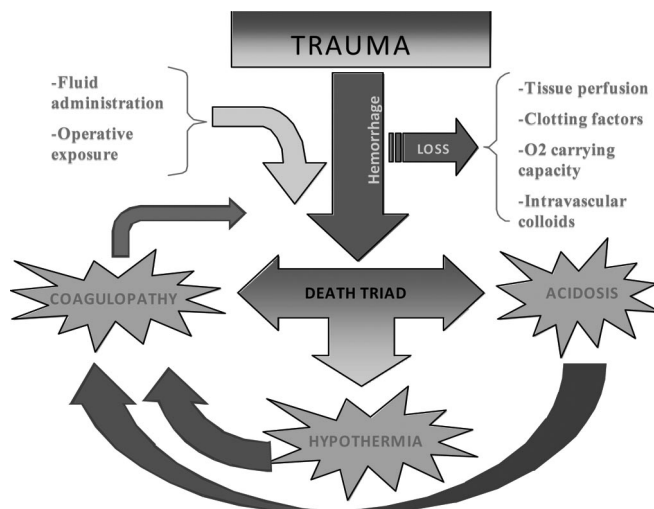
it has been shown to correlate with severity of shock.<sup>66,67</sup> Rutherford et al.<sup>68</sup> showed that a base deficit of 8 carried a 25% mortality for patients older than 55 years with no head injury or younger than 55 years with a head injury. When it remains increased during attempted resuscitation, it should be taken as a sign that adequate cellular oxygenation may not yet have been achieved. Its largest drawback lies in the fact that it can be elevated in other situations besides underresuscitation, particularly renal dysfunction and hyperchloremia. The latter is especially prevalent in patients who have received large amounts of normal saline or HTS with a consequent hyperchloremic acidosis. Nevertheless, the base deficit is a useful guide to the adequacy of resuscitation efforts in the early stages.

Lactate is a byproduct of anaerobic metabolism and a fairly specific marker for tissue hypoperfusion. Although its clearance is a matter of some controversy, most believe that it has a half-life of ~3 hours. It has been shown to be a predictor of mortality and serial measurements of the serum lactate serve as a useful guide for the adequacy of resuscitation efforts.<sup>69–73</sup> Its largest drawbacks consist of the fact that the value takes longer to obtain than a blood gas and it must be drawn from an arterial or central venous source (to avoid sampling of a region rather than the whole body). It is worth remembering that lactate is partially cleared through the liver, making it of much less utility in patients with liver failure or cirrhosis or both because their levels can be elevated even in the face of adequate resuscitation.

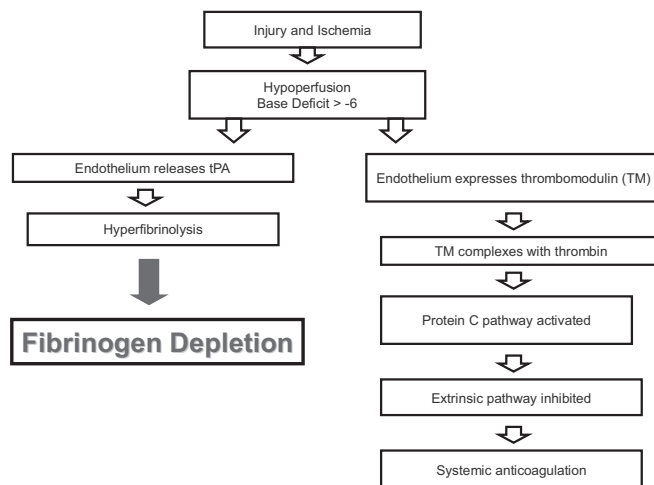
### UNDERSTANDING TRAUMA-INDUCED COAGULOPATHY

The coagulopathy of trauma is one of the single most accurate predictors of prognosis in trauma and is one of the most significant challenges to any DCR effort. Coagulopathy in trauma is very common, and several retrospective reviews have documented an incidence as high as 25% to 30%.<sup>74,75</sup> The incidence of coagulopathy becomes even more prominent as the severity of injury increases. Well more than half of patients with ISS of 45 to 59 are coagulopathic, whereas 80% to 100% of patients with head injury with Glasgow Coma Scale score <6 show some signs of coagulopathy.<sup>76</sup> Although many factors have been proposed to play a role in the development of coagulopathy in trauma patients, for the most part, it is suggested tissue hypoperfusion in combination with severe tissue injury and not the mechanism of injury that influences the development of coagulopathy during massive transfusion.<sup>77</sup> Although coagulopathy is one of the most preventable causes of death in trauma, it has been implicated as the cause of almost half of hemorrhagic deaths in trauma patients.<sup>78</sup> A study by MacLeod et al.<sup>75,79</sup> demonstrated that an initial abnormal PT increases the adjusted odds of dying by 35% and an initial abnormal PTT increases the adjusted odds of dying by 36%.

Along with environment and blood loss, there are several other mechanisms that have been proposed to explain the development of coagulopathy seen immediately after a traumatic insult and in the ensuing resuscitation. In the first few minutes posttrauma, tissue hypoperfusion can cause



**Figure 1.** Components involved in the development of the coagulopathy of trauma.



**Figure 2.** Trauma-induced coagulopathy.

inflammatory and metabolic changes, most evidenced by acidosis, which can affect the efficacy of the innate coagulation system.<sup>74</sup> In a review of current literature, Lier et al.<sup>80</sup> suggest that there is notable impairment of hemostasis once a patient's pH reaches 7.1 or below. This acidosis and coagulopathy in addition to hypothermia are the cornerstones of the infamous “triad of death” (Fig. 1). Hess et al.<sup>81</sup> suggests six primary mechanisms involved in the induction of traumatic coagulopathy including tissue trauma, shock, hemodilution, hypothermia, acidemia, and inflammation.

Moreover, as platelets and coagulation factors begin to be used, a consumptive coagulopathy takes effect as well.<sup>82</sup> This involves endothelial-mediated fibrinolysis and the activated protein C pathway (Fig. 2). As mentioned previously, hypothermia begins to have an impact on the body's ability to alter fibrin and form clots. Other processes such as metabolic acidosis, hypocalcemia,<sup>83</sup> increased fibrinolysis,<sup>82</sup> and the inappropriate breakdown of formed clots by physical manip-

ulation of the wounds, all contribute to bleeding dyscrasias.<sup>84</sup> It is important to note that many of these coagulopathic changes occur early after trauma; thus by the time damage control measures are undertaken, the coagulation abilities of the severely injured patient can already be compromised. This highlights the importance of early and definitive initiation of measures to correct coagulopathy. In severely injured patients coagulopathy, coagulopathy can be exacerbated during initial care, resuscitation, and stabilization. IV fluids and packed red blood cells (PRBCs) alone, although routinely administered as part of normal resuscitation procedures and advanced life support measures, can dilute the concentration of clotting factors in the blood. This dilutional coagulopathy is well described.<sup>2,56,85</sup> In 2003, Hirshberg et al. used computer modeling to calculate the changes in PT, fibrinogen, and platelets that occurred with hemodilution. Among their key results were the findings that more than 5 units of PRBCs will lead to a dilutional coagulopathy, that prolongation of the PT was a sentinel sign of dilutional coagulopathy, and that this phenomenon occurs early. Hirshberg et al. proposed that measures should be undertaken in an early and aggressive manner to prevent this dilutional coagulopathy before the PT becoming subhemostatic. They proposed doing so by using fresh frozen plasma (FFP) in a 2:3 ratio (FFP:PRBCs) during the course of resuscitation.<sup>86</sup>

### A Blood- and Coagulation Factor-Based Resuscitation Strategy

It should be mentioned that the majority of trauma patients do not require DCR and that its techniques should be reserved for those who are the most severely injured. For these patients, however, the rapid and aggressive use of techniques to identify and control bleeding and coagulopathy is essential. Therefore, it is paramount that these patients be quickly and reliably identified. Early identification of the patient at risk for massive transfusion may be of use to direct rapid correction of coagulopathy, acidosis, and hypothermia. This will facilitate early mobilization of blood bank resources.

Several methods can be useful in identifying patients at risk and revolve on the early identification of shock. In most patients, the combination of altered mental status, cool/clammy skin, and an absent radial pulse is a well-established triad, indicating hypovolemic shock.<sup>25</sup> When examining vital signs, the shock index (i.e., the ratio of heart rate to SBP) is a better indicator of shock than hypotension and is more sensitive than individual vital signs analysis.<sup>87</sup> An attempt to identify effective predictors of the need to initiate prehospital interventions was proposed by Holcomb et al.,<sup>11</sup> who reported that the character of the radial pulse combined with the motor and verbal score of the Glasgow Coma Scale reliably stratified patients. Nunez et al. described an additional method of identification, ABC, a scoring method based on four parameters: penetrating mechanism, positive focused assessment sonography for trauma, SBP less than or equal to 90 mm Hg on arrival, and heart rate greater than or equal to 120 bpm on arrival. In this scoring method, a score of 2 or greater is 75% sensitive and 86% specific for predicting massive transfusion.<sup>88</sup> In addition, laboratory findings indicative of hypoperfusion include bicarbonate, base deficit, and

lactate.<sup>87</sup> Of these, lactate has been demonstrated to have the best association with hypovolemic shock and death and is a useful marker as an endpoint of resuscitation.<sup>10</sup>

The diagnosis of coagulopathy can frequently be made clinically, as coagulopathic patients will demonstrate generalized nonsurgical bleeding from wounds, serosal surfaces, skin edges, and vascular access sites.<sup>1</sup> Unfortunately, the coagulopathy is generally in an advanced state under these circumstances. Using laboratory tests to diagnose coagulopathy results in unacceptable delays, and point-of-care devices have yet to be validated in trauma. The classical measures of coagulation have their own shortcomings. PT and PTT will show disorders of plasma coagulation but will miss platelet dysfunction and hyperfibrinolysis.<sup>75</sup> These tests can sometimes take hours to complete if there is no availability to point-of-care devices and have been noted to have poor correlation with clinical bleeding.<sup>89</sup> Furthermore, PT will not identify coagulation deficiencies caused by hypothermia as PT is determined in the laboratory at a standard temperature of 37°C, which masks temperature effects on enzyme activities.<sup>12</sup> Another laboratory measure for coagulation status is the activated clotting time, which tests overall coagulation status. In one trial that used clinical coagulopathy as the standard a single elevated activated clotting time above 160 seconds carried a sensitivity of 71% and specificity of 96%.<sup>89</sup>

Despite the extreme importance of early identification, standard assays are often inadequate in diagnosing clotting deficiencies.<sup>90,91</sup> These assays serve mainly as a measure of time to clot initiation.<sup>92</sup> Because the most commonly used assays for clotting efficacy, PT, and PTT are performed on platelet-poor plasma, they are unable to assess the interactions that occur between clotting factors and platelets as clot forms.<sup>93</sup>

Thromboelastography (TEG) is a simple test that can broadly determine coagulation abnormalities and give information about fibrinolytic activity and platelet function that is not available from routine coagulation screens.<sup>2</sup> Its use during cardiopulmonary bypass surgery for the detection of coagulopathy has improved accuracy in diagnosing hemostatic abnormalities.<sup>92</sup> In contrast, although studies with blunt trauma patients have illustrated a correlation between TEG readings and eventual transfusion requirements, this test is largely underused in the identification of coagulopathy in trauma patients.<sup>93</sup>

The parameters analyzed on a TEG tracing, the thromboelastogram, produce a more comprehensive illustration of the clotting cascade than is provided by currently used laboratory values.<sup>90,94</sup> Because it is known which blood components are responsible for the phases of clot formation, irregularity in a specific portion of the TEG serves a diagnostic purpose. These values may direct transfusion of appropriate blood components and drugs, including rFVIIa, for treatment of specific clotting deficiencies. A normal TEG in the presence of abnormal vital signs may indicate surgical bleeding and the need for exploration.<sup>90,95</sup> This could, theoretically, reduce transfusion requirements of patients arriving in emergency departments, as it has for patients undergoing cardiopulmonary bypass.<sup>95,96,97</sup>

Algorithms directing transfusion have proven to significantly reduce blood product use in cardiopulmonary bypass.<sup>92,95</sup> This technology has recently been applied to the description of the coagulation profile of the trauma patient. Based on the TEG parameters, data from studies of blunt trauma patients have indicated that these patients are hypercoagulable at admission.<sup>1,91</sup> Using this technology, it has been revealed that those patients with the most severe injuries, as characterized by greater ISS, tend to be hypocoagulable.<sup>1,2</sup> This novel modality has yet to be fully validated in trauma hemorrhage, and some devices are user dependent, as is interpretation of the resultant thromboelastograms.<sup>98</sup> Currently, the surgeon's clinical assessment of the blood loss and resultant coagulopathy are the mainstay for the initiation of a blood and blood product resuscitation. Future standardized triggers may involve operative blood loss, number of transfused units, or some of the earlier mentioned testing modalities but are not yet substantiated.

## DAMAGE CONTROL RESUSCITATION

### Resuscitation With FFP

DCR helps manage the coagulopathy of trauma through the early and aggressive administration of blood products to the severely injured trauma victim. In a recent review of a combat support hospital experience, it was found that the majority of trauma can be managed with standard crystalloid-based resuscitation techniques, advocated by Advanced Trauma Life Support since the 1960s.<sup>25,83</sup> However, hemorrhage accounts for 40% of all trauma-associated deaths.<sup>99</sup> Theoretically, early and sustained administration of FFP can help to correct the state of depleted coagulation factors common in the bleeding patient. A unit of FFP contains ~0.5 g of fibrinogen and all the pro- and anticoagulant proteins of blood.<sup>84</sup>

In 1985, retrospective review of Hewson et al.<sup>100</sup> of 68 massively transfused patients found that coagulopathy was common after crystalloid administration and that PTT correlated with the volume of crystalloids given. He recommended that FFP and PRBCs be given at a ratio of 1:1. For nearly two decades, this recommendation was largely ignored. However, in 2002, although describing the effect of fluids on coagulation, Hirshberg et al.<sup>86</sup> concluded that to avoid coagulopathy, RBCs and FFP must be given in a 3:2 ratio. This has evolved to the use of a 1:1 FFP to PRBC ratio, which is based largely on the evidence acquired during the military's recent experience with the management of combat casualties. Borgman et al. compared mortality rates associated with varying ratios of FFP to PRBC in the management of trauma seen in the Iraq conflict. They found that patients receiving a "high" ratio of FFP to PRBC (1:1.4) had the lowest overall mortality rates and hemorrhage-related mortality rates and concluded that high FFP to RBC ratio is independently associated with improved survival to hospital discharge.<sup>83</sup> Similar results were found by Duchesne et al.<sup>101</sup> in a retrospective analysis of a civilian trauma center population requiring surgery receiving >10 units of PRBCs. A significant difference in mortality (26% vs. 87.5%) when FFP: PRBC ratio was 1:1 versus 1:4 ( $p = 0.0001$ ) was observed. These data suggest that, in

trauma requiring massive transfusion, an FFP:PRBC in a ratio of 1:1 confers a survival advantage compared with those transfused with a lower ratio.

In prior years, trauma transfusion protocols typically did not include a specific ratio of FFP to PRBCs, often only transfusing FFP after the PT/PTT became significantly prolonged or after a fixed number of PRBCs were transfused.<sup>83,102,103</sup> The institution of ratio-based massive transfusion protocols (MTPs) have produced studies that suggest efficacy.

Biffi et al.<sup>104</sup> examined the performance of an MTP that included early FFP administration and found that this was associated with a significant decrease in the incidence of death caused by exsanguination from 9% to 1%. Another study demonstrated a massively transfused patient population (>50 units of blood in the first 24 hours) with a 43% survival rate and 84% the survivors discharged home or to a rehabilitation hospital.<sup>105</sup> These ideas seem to have gained acceptance. In 2005, Malone et al.<sup>85</sup> polled trauma surgeons around the country that the majority of whom thought the optimal ratio of FFP to PRBC was 1:1 and that this should be given early in the course. Another important observation is that patients who received low or medium FFP to RBC ratios died predominantly of hemorrhage at a median of 2 hours to 4 hours<sup>83</sup> and computer simulation models suggest that most bleeding trauma patients will need FFP well before losing one blood volume.<sup>84</sup>

Early and sustained administration of FFP may help to correct the state of depleted coagulation factors common to the bleeding patient. However, there are logistical obstacles to providing FFP to a trauma patient as rapidly as it is needed. By definition, FFP is plasma that is frozen at -18°C within 8 hours of being drawn from the donor. The advantage of freezing plasma in this manner is that all coagulation factors are preserved at their in vivo activity levels and remain stable during storage. Unfortunately, thawing FFP takes 20 minutes to half an hour; so, it cannot always be available to a massively hemorrhaging patient during the crucial first minutes of DCR.

Alternative plasma products, such as thawed plasma and liquid plasma, are stored in liquid form and can be provided to a trauma patient immediately, without the need to thaw them. Some loss of clotting factors occur when plasma is stored in liquid form, particularly loss of the "labile" factors V and VIII. Thawed plasma can be considered equivalent to FFP. It is stored in liquid form for a maximum of 5 days after it is thawed. At the end of 5 days, coagulation factors other than factors V and VIII maintain 70% to 80% of their original activity levels, and the fibrinogen level is unchanged. The levels of factors V and VIII are reduced to ~65% activity, still within the hemostatic range.<sup>106</sup>

With a 5-day shelf life, it can be difficult to keep an adequate supply of thawed plasma on hand, particularly plasma of the scarce "universal donor" type AB. Another option is liquid plasma, which has a shelf life of 26 days or 40 days, depending on the preservative that is used. Here, the loss of factors V and VIII activity becomes more significant. At 26 days, fibrinogen and most coagulation factor levels are virtually unchanged. Factor V has ~35% of its original



activity at 26 days, which is still within the hemostatic range. Factor VIII activity declines to ~10%.<sup>107</sup> Factor VIII is provided in cryoprecipitate, which may be used to augment the activity of liquid plasma. A reasonable policy in a busy trauma center would be to keep type AB thawed plasma or liquid plasma available for the initial DCR. Thawed, type-specific FFP can then be provided once the patient's blood type has been determined and the FFP has been thawed.

## Resuscitation With Blood

As part of the DCR protocol described by Holcomb et al.,<sup>11</sup> the most severely injured patients receive fresh whole blood (FWB) as a resuscitative fluid. FWB was historically used in transfusion until it fell out of favor in the middle of the twentieth century because of its side effects and the convenience provided by component therapy for treating other nontraumatic diseases. By the late 1980s, component therapy had almost completely replaced whole blood therapy.<sup>24</sup> However, recent military accounts of the utilization of FWB have emerged, noting its usefulness either when component therapy has failed or when logistically it was the most feasible option. During the battle of Mogadishu, 120 units of FWB were drawn, and 80 units were administered.<sup>51</sup> FWB was also the main blood product when platelets were depleted during the first Gulf War and when profoundly coagulopathic casualties presented in Bosnia and Kosovo.<sup>108</sup>

Theoretically, FWB replaces all the blood components lost to trauma, including platelets and fully functional clotting factors. In addition, the components of FWB are more functional than their stored counterparts. Separating blood into components results in dilution and loss of about half of the viable platelets (88K/ $\mu$ L in 1 unit of component therapy vs. 150–400 K/ $\mu$ L in 500 mL of FWB), PRBCs (hematocrit 29% in component therapy vs. 38–50% in FWB), and clotting factors decreasing the coagulation activity of the separated components to 65% when giving a 1:1:1 ratio of component therapy.<sup>51,109</sup> Thus, the integrity and flow characteristics of PRBC are compromised because of metabolic depletion and membrane integrity loss.<sup>108</sup> FWB skips the steps of separation and storage and allows for better hemostasis (a single unit of FWB has a hemostatic effect similar to 10 units of platelets).<sup>110</sup> Logistically, FWB provides the advantage of being readily available and requires no delay for thawing but requires the presence of a ready and willing donor pool. In a forward deployed military hospital in Iraq, transfusion with FWB resulted in significant improvements in both hemoglobin concentration (9.0–10.7 g/dL) and coagulation parameters (international normalized ratio: 2.0 to 1.6).<sup>108</sup> Further investigation of blood components may lead to additional refinement of the 1:1:1 (PRBC, platelets, and FFP) approach currently used in civilian trauma centers.

It bears mentioning that transfusion, with FWB or component therapy, is associated with risks, which should be weighed when deciding whether or not to transfuse a patient. The observation that transfusion is associated with increased mortality, even when controlled for other risk factors, has been well documented.<sup>11,111,112</sup> In addition, we have come to have an appreciation for the entity of transfusion-related acute lung injury (TRALI), which occurs in 1 in every

100,000 transfusions and is now the leading cause of mortality after blood product administration. TRALI is a life-threatening antibody mediated event, most often seen during the administration of FFP.<sup>113</sup> Recently, an entity-coined delayed TRALI syndrome has been described, occurring 6 hours to 72 hours posttransfusion in up to 25% of critically ill patients.<sup>114</sup> Delayed TRALI is associated with the time the blood components are stored before use, thus transfusing FWB, in theory, can decrease the likelihood of this complication. Other complications include multiple organ failure because of immunogenic transfused cells or infection.<sup>115</sup> Claridge et al.<sup>116</sup> demonstrated that infection rates were >four times more likely in transfused patients than in those who did not receive transfusion. Considerable debate exists on whether these differences exist because of the adverse effects of transfusion or because transfusing the blood products allows patients to live long enough to experience these complications. Some authors maintain that the increased mortality, time spent in the ICU, and length of hospital stays associated with blood product administration is evidence enough to implicate transfusion products,<sup>111</sup> whereas others note that at the very least, the picture is unclear.<sup>71,112</sup> At this point, data from randomized prospective trials is needed to provide a more detailed picture regarding transfusion complications, the most advantageous ratio of blood components, and the possibility of FWB in civilian trauma centers.

## Additional Components

### Platelets

Although most believers in DCR agree on the need for early administration of FFP, debate still exists on the need for platelets. Several of the landmark studies on blood product ratios mention the use of 1:1:1 (FFP to PRBC to platelets).<sup>56,85,86</sup> The rationale for doing so is simple: platelets are easy to administer, do not require thawing similar to FFP, and produce a readily measurable effect on coagulation by immediately increasing the absolute platelet count.<sup>56</sup> Studies have shown the application of platelets in a 1:1:1 ratio decrease mortality in trauma patients. The study by Gunter et al.<sup>117</sup> classified patients into two groups, either receiving a ratio >1:5 or <1:5, noting a decreased 30-day mortality in those receiving a ratio of 1:5 or greater as compared with those who received a ratio <1:5 of platelets:PRBC. The same year, Holcomb et al. looked at ratios of platelet:PRBC, FFP:PRBC, and combinations of each, classifying high (>1:2) and low (<1:2) ratios for each platelets and FFP to PRBC. This study found improved 30-day survival in groups with high ratios of platelet:PRBC and those with high ratios of FFP:PRBC. They then looked at four groups of patients receiving either high FFP and high platelet ratios, high FFP and low platelet ratios, low FFP and high platelet ratios, and low FFP and low platelet ratios, noting the high FFP and high platelet group had significantly increased survival at 6 hours and 24 hours and 30 days compared with the other groups.<sup>118</sup> However, problems exist concerning the efficacy of platelet administration. Platelets lose a degree of their functionality when stored<sup>82</sup> via a decrease in expression of high affinity

thrombin receptors.<sup>1</sup> Although absolute platelet count has a readily available measurement, there is no way of knowing how many transfused platelets are restored to full functionality.<sup>82,119</sup> Indeed, some recent data suggest that a close intraoperative ratio of 1:1:1 of FFP to PRBC to platelets during early hemostatic resuscitation might have no effect on mortality rate.<sup>110</sup> One must note, however, all of these studies look at platelets intraoperative and not in early resuscitation. In reality, platelets are the last thing to reach the patient because of the way MTPs are written. To determine the true benefit of close ratio administration of platelets on mortality, the platelets would ideally be given in a 1:1:1 ratio before the patient is brought to the OR.

There are some potential down sides to platelet transfusion. Massive blood transfusion is an established risk factor for ALI/ARDS.<sup>120</sup> An extensive study of medical ICU patients at the Mayo Clinic has shown that the transfusion of any type of blood product, and particularly plasma-rich blood products (platelets and FFP), is associated with ALI in critically ill medical patients.<sup>121</sup> Platelet transfusions can cause life-threatening TRALI.<sup>122</sup> MSOF can also be caused by trauma-related platelet and plasma transfusions.<sup>123</sup> The two-insult model of posttrauma MSOF involves the priming and activation of neutrophils and production of platelet-activating factor in severely injured patients, plus the generation of lysophosphatidylcholines and other biologically active products in stored blood components. The stored cellular membrane breakdown products can act as a potent stimulant to enhance neutrophil activation in the patient.<sup>124</sup> The two-hit combination of trauma and transfusion can enhance priming and activation of neutrophils cytotoxicity in the patient and lead directly to endothelial cell damage and multiple organ failure.

In addition, the effectiveness of transfusing platelets in a patient with coagulopathy is questioned by the new cell-based model of trauma-induced coagulopathy, which suggests thrombomodulin, produced by endothelium, complexes with thrombin to create anticoagulant thrombin, inhibits the cleavage of fibrinogen into fibrin and activates protein C leading to decreased inhibition of fibrinolysis.<sup>125,126</sup> Any augmentation of the clotting pathway theoretically adds to the production of thrombomodulin and paradoxically prevents clot formation. This suggests, in addition to platelets, other coagulation factors need to be addressed to treat coagulopathies in trauma patients.

As a practical matter, platelets tend not to be critically low in the earliest phases of hemorrhagic shock, although they might not be fully functional.<sup>84</sup> It may be appropriate to attend to the hypothermia, acidosis, and coagulopathy because of clotting factor derangement first, then address the platelets at a somewhat later stage of the resuscitation. There exists compelling evidence that providing PRBC and plasma in a 1:1 ratio can be life saving in the earliest stages of DCR, but as discussed above, the evidence is not as clear regarding the addition of platelets in a 1:1:1 ratio with PRBC and plasma. ALI or multiple organ failure would be a devastating complication of DCR for severe trauma. Studies regarding platelets qualitative

function and clot strength during early hemostatic resuscitation and studies looking at preoperative platelet administration are still needed. One must carefully consider the risk-benefit ratio before deciding to expose the trauma patient to an increased risk of these complications.

### Cryoprecipitate

DCR protocols that provide PRBC and plasma in a 1:1 ratio or PRBC, plasma, and platelets in a 1:1:1 ratio are directed toward replacing what the bleeding trauma patient is losing, i.e., whole blood. A decision to transfuse cryoprecipitate falls into a different category: it gives an extra bolus of certain plasma factors that are already being provided in the plasma units. Cryoprecipitate is made by putting FFP through a freeze-thaw process that precipitates out a concentrated product (the “cryoprecipitate”) that consists of fibrinogen, von-Willebrand factor, factors VIII and XIII, and fibronectin.<sup>127</sup> Thus, the question of whether to include cryoprecipitate in a DCR protocol depends on whether it is beneficial to give hemorrhaging trauma patients supranormal amounts of those five factors.

There is some uncertainty regarding whether prophylactic administration of cryoprecipitate should be included in DCR protocols.<sup>84</sup> Fibrinogen—that is, factor I—tends naturally to be the focus of attention in the debate. Fibrinogen is an acute phase reactant.<sup>128</sup> The liver produces tremendous amounts of fibrinogen during traumatic bleeding. As a result, trauma patients rarely arrive in the ER with low fibrinogen levels. Therefore, cryoprecipitate would only be needed in a patient with advanced liver failure<sup>129</sup> or a congenital fibrinogen defect.

When considering whether cryoprecipitate should be included in a DCR protocol, it is instructive to think numerically. It is generally agreed that the patient’s fibrinogen level during severe hemorrhage should be kept above 100 mg/dL. Assuming an average adult plasma volume of 3,000 mL and starting with a fibrinogen level of 0, the addition of 3,000 mg of fibrinogen would result in the desired fibrinogen level of 1 mg/mL or 100 mg/dL—at least, until it is consumed by clot formation. A 200-mL to 250-mL unit of FFP contains ~400 mg of fibrinogen, and 1:1 plasma to red cell DCR protocols typically deliver at least 6 units of plasma in every cooler. Thus, ~2,400 mg of fibrinogen are delivered in every cooler by the FFP alone. Even if the patient suffered from congenital afibrinogenemia, the DCR would come relatively close to replenishing the full 3,000 mg with each trauma cooler.

Of interest, a bag of cryoprecipitate has a volume of ~10 mL to 15 mL and contains ~250 mg of fibrinogen. Ten bags of cryoprecipitate are usually pooled together in each dose. Thus, one dose of cryoprecipitate has a volume of ~150 mL and contains 2,500 mg of fibrinogen. Therefore, the six units of FFP provided in each trauma cooler deliver about the same amount of fibrinogen as a single 150-mL dose of cryoprecipitate. At present, the question of whether it is desirable to supplement the DCR transfusion protocol with regular 2,500 mg doses of fibrinogen in cryoprecipitate remains a matter of clinical judgment.

## Recombinant Factor VIIA

Part of the DCR sequence as proposed by Holcomb<sup>130</sup> involves the use of rFVIIa with the very first units of red cells and plasma and as needed throughout the resuscitation. Although the mechanism of action for levels of rFVIIa used in trauma patients is not fully elucidated, at pharmacologic doses, it is thought to activate factor X, which activates the common pathway that generates a fibrin plug.<sup>131</sup> The rFVIIa is currently only approved by the FDA for the treatment of hemophilia, with all trauma uses being off-label. Nevertheless, there are several studies of note that have been performed with the aim of demonstrating its safety and efficacy. For several years, all studies done on rFVIIa comprised retrospective and anecdotal case series describing the drug's effects on bleeding patients. Martinowitz et al.<sup>132</sup> noted that rFVIIa caused cessation of bleeding, decreased need for further transfusion, and shortened PT/PTT in seven massively transfused, coagulopathic patients after conventional therapy failed. Three years later, Khan et al.<sup>133</sup> observed that lower doses showed similar results as higher doses in an 8-month retrospective cohort study with 13 patients. Similar results were duplicated in subsequent studies.<sup>134</sup> A review of animal studies describing the safety of rFVIIa was published in 2005, which highlighted the safety of the drug in multiple animal trials and suggested that rFVIIa is not associated with increased thrombotic complications.<sup>135</sup>

In 2004, Dutton et al. reported what was the best evidence to date describing the effects of rFVIIa in trauma, presenting data from 81 patients compared with "control patients" from the trauma registry. These data demonstrated a reversal of coagulopathy and a reduction in PT.<sup>136</sup> Of concern, however, was their finding of a higher mortality in patients who were administered rFVIIa even though the mortality rate was controlled for specific injuries, admission lactate, and predicted probability of survival.<sup>136</sup>

Evaluating the true effect of rFVIIa on mortality was extremely difficult because most of these studies were administering rFVIIa as a last resort. These limitations were finally addressed in 2005 when Boffard et al. published the results of a two-armed, randomized, placebo controlled, double-blinded trial to examine the effect of rFVIIa in the control of bleeding in severely injured trauma patients. One arm of the trial evaluated its use in blunt trauma whereas the other assessed its utility in penetrating trauma. Although there was no change in mortality, the trial demonstrated a statistically significant reduction in transfusion required in the blunt trauma group, whereas the results for the penetrating trauma group showed no benefit.<sup>137</sup> In addition, the trial demonstrated the safety of rFVIIa at the tested doses.<sup>137</sup> Another randomized clinic trial conducted in a cohort of patients requiring pelvic surgery demonstrated no significant reduction in transfusion requirement.<sup>138</sup>

Two other trials have been conducted attempting to determine conditions of futility regarding rFVIIa administration.<sup>139,140</sup> Both of these trials were retrospective reviews with no randomization. A multicenter, multinational randomized, controlled trial studying the efficacy of rFVIIa after trauma is currently ongoing with strict eligibility criteria. The

true effects and risks associated with rFVIIa still need to be studied, although recent data would indicate that its hemostatic properties make it an important addition to the damage control sequence.

Although rFVIIa has shown some promise in correcting coagulopathy in blunt trauma patients, the function of rFVIIa is decreased in acidotic states. Meng et al.<sup>64</sup> noted that pH strongly affected the activity of factor VIIa, reducing the enzyme's activity by 90% as the pH decreased from 7.4 to 7.0. However, this study is limited by the fact it was performed in the laboratory setting with platelets from healthy volunteers. This idea of decreased efficacy of rFVIIa in acidotic conditions is concerning as acidosis is a common issue in trauma patients.

Another key point that must be addressed when considering use of rFVIIa in patients requiring massive transfusion comes from insights into coagulopathy associated with the use of this material. In the contemporary cell-based model of coagulation, the underresuscitated trauma patient is at risk for accelerated coagulopathy with administration of rFVIIa through binding of thrombin to thrombomodulin and activation of protein C and protein S. Thus, in the setting of trauma, rFVIIa is best given to patients who are fully resuscitated and have appropriate levels of all clotting factors available. Administration of rFVIIa in the setting of injury is not a substitute for administration of other required blood products.

A need still remains for further study of rFVIIa usage in trauma patients. From the available literature, rFVIIa seems to be safe and possibly decreases transfusion in blunt trauma.<sup>141</sup> However, rFVIIa has not shown any efficacy in penetrating trauma. Furthermore, no study has looked at different dosing regimens, timing of dosage, or risk/benefit analysis. More information is necessary before recommendation for usage of rFVIIa in a traumatic setting can be defined. Major decreases in the efficiency of rFVIIa in patients with severe metabolic derangement necessitate further investigation, and there still remains a need for further study to address dosing, timing, and risk/benefit in the trauma patient with major hemorrhage.

## DAMAGE CONTROL SURGERY

The main premise of damage control surgery is that the metabolic derangement of ongoing bleeding supersedes the need for definitive operation. As such, the main thrust of damage control surgery is the rapid surgical control of bleeding. The recognition of the importance the metabolic distress seen after major trauma has changed the care for the severely injured patient. Victims of penetrating torso trauma or multiple blunt trauma with hemodynamic instability are generally better served with abbreviated operations that control hemorrhage allowing for subsequent focus on resuscitation, correction of coagulopathy, and avoiding hypothermia. As such, these surgeries tend to have a high complication rate, as survival is given a higher priority than morbidity, in these patients who are in poor physiologic condition.<sup>2</sup>

After resuscitation and transport to the OR, damage control surgery consists of three phases as described by Feliciano et al.<sup>142</sup> in 1988—initial operation with hemostasis

and packing, transport to the ICU to correct the conditions of hypothermia, acidosis, and coagulopathy, and a return to the OR for definitive repair of all temporized injuries.

In the case of laparotomy, once a damage control approach has been initiated, the initial procedure is directed toward controlling surgical bleeding and thereafter containing spillage from the alimentary and urogenital tract.<sup>143</sup> A rapid midline incision is made, hemoperitoneum and clots are removed, and the abdominal cavity is quickly surveyed.<sup>144</sup> Bleeding is controlled with either ligation of vessels, balloon catheter tamponade, or packing. Packing was originally described by Pringle in 1908. Despite falling out of favor over infectious concerns decades ago, the technique has seen resurgence in utilization. Since the formalization of damage control surgery in the 1980s by Feliciano, Rotondo, and others, packing has remained a mainstay of damage control surgery. Definitive repair at this phase is deferred; instead, only expedited interventions that are absolutely necessary to control hemorrhage and contamination are undertaken.<sup>51</sup> Splenic and renal injuries are treated with rapid resections, nonbleeding pancreatic injuries are simply drained, and liver injuries are packed. Large vessel venous injuries, including even the inferior vena cava, can be treated with ligation. Arterial injuries, which, in the past, would have been treated with an interposition graft or patch repair, are temporized with the placement of shunts, with definitive repair to follow as the patient's metabolic condition permits. The treatment of hollow viscus perforations includes either a simple suture closure or rapid resection of the involved segment. No anastomoses are performed, and ostomies are not matured. These can be done at a later time once the patient's condition has stabilized.

Once surgical bleeding is controlled, the fascia is left open.<sup>2</sup> The skin can be closed with either towel clips<sup>10</sup> or with a running monofilament suture. If visceral edema is too great to allow for skin closure, any number of prosthetic devices can be rapidly sewn to the skin edges such as IV bags and x-ray cassette drapes. Also used extensively is any number of vacuum dressings. These devices have the advantage of keeping the patient dry, decreasing the workload of the ICU nursing staff, and allowing quantification of any ongoing blood loss. At the completion of this portion of the procedure, the patient can either be transported to the ICU or to the interventional radiology suite for embolization of arterial hemorrhage that could not be controlled during the open procedure, such as pelvic fracture or liver trauma involving the arterial circulation.

Techniques are also available for the rapid control of bleeding in other body regions. The damage control thoracotomy for pulmonary injury typically involves rapid tractotomy with suture ligation of bleeding vessels and rarely involves formal pulmonary resection.<sup>145</sup> Injury to the hilum will usually require pneumonectomy for rapid control of hemorrhage. Extremity trauma in the patients with multiple injuries usually involves ligation of venous injury and shunting of major arterial injury with rapid external fixation for orthopedic stabilization.

After control of bleeding in the OR, the traditional damage control sequence next involves transport to the ICU for physiologic stabilization. Ventilation is maintained making use of pressure-regulated or volume control modes aimed at maintaining low peak inspiratory pressures to help prevent ALI. Fraction of inspired oxygen (FIO<sub>2</sub>) is originally set at 100% and is weaned to keep oxygen saturations >93%.<sup>146</sup> Hypothermia is corrected both passively and actively, whereas FFP and factor VII are administered to address coagulopathy. Acidosis should correct itself as the delivery of oxygen is optimized.

Damage control surgery has led to better than expected outcomes in these grievously injured patients. One report from Iraq noted that damage control laparotomies allowed for a 72.8% overall survival rate.<sup>51</sup> Another study examining the evolution of damage control techniques and outcomes over 10 years noted that patients who received damage control surgery for penetrating abdominal trauma at the end of that time period boasted higher survival rates and a decreased incidence of OR hypothermia.<sup>147</sup> Other techniques and innovations, which could account for these improved outcomes, include earlier initiation of damage control measures, goal directed resuscitation, appropriately warming the OR, anticipating blood loss, and avoiding overresuscitation.<sup>148</sup>

## CONCLUSION

The concept behind DCR is to stop life-threatening hemorrhage and use resuscitative measures to quickly stave off the conditions that prolong hemorrhagic shock. DCR focuses on early, aggressive correction of the components of the lethal triad, hypothermia, coagulopathy, and acidosis. This strategy must start in the ER and continue through the OR and ICU until the resuscitation is complete. Consideration should be given to the following components of DCR.

Permissive hypotension may be of to patients in hemorrhagic shock. A systolic pressure of 90 mm Hg can theoretically avoid the complication of rebleeding but still maintain perfusion of vital structures. The use of isotonic crystalloids should be kept to a minimum as they have numerous detrimental effects. Rather, the replacement of lost blood volume should be accomplished with transfusion of PRBCs and component therapy via the institution of an effortless, multidisciplinary MTP. Ideally, a nearly equal FFP:PRBC transfusion ratio is initiated early, and resuscitation efforts are guided by the early and continued determination of lactate and base deficit levels, coagulation studies, and platelet count. The use of rFVIIa in conjunction with the above measures has proven safety but is not FDA approved for use in trauma. FWB transfusion is currently primarily limited to the most severely injured military combat casualties. One must remember that these resuscitation techniques are performed in conjunction with the damage control surgery principles of rapid surgical control of bleeding and contamination and abbreviated operation. Resuscitation efforts of any kind will be futile without control of actual surgical bleeding, and the concept of temporizing surgery over definitive surgery is of paramount importance.

DCR and surgery are the new way of approaching the age old problem of hemorrhagic shock, which remains the leading cause of death in the trauma patient. These new concepts and techniques require further study and refinement but show promise for the improving the care of the severely injured trauma patient.

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