



# Traumatic coagulopathy-Part 2: Resuscitative strategies

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## Abstract

**Objective** – To discuss the current resuscitative strategies for trauma-induced hemorrhagic shock and acute traumatic coagulopathy (ATC).

**Etiology** – Hemorrhagic shock can be acutely fatal if not immediately and appropriately treated. The primary tenets of hemorrhagic shock resuscitation are to arrest hemorrhage and restore the effective circulating volume. Large volumes of isotonic crystalloids have been the resuscitative strategy of choice; however, data from experimental animal models and retrospective human analyses now recognize that large-volume fluid resuscitation in uncontrolled hemorrhage may be deleterious. The optimal resuscitative strategy has yet to be defined. In human trauma, implementing damage control resuscitation with damage control surgery for controlling ongoing hemorrhage, acidosis, and hypothermia; managing ATC; and restoring effective circulating volume is emerging as a more optimal resuscitative strategy. With hyperfibrinolysis playing an integral role in the manifestation of ATC, the use of antifibrinolytics (eg, tranexamic acid and aminocaproic acid) may also serve a beneficial role in the early posttraumatic period. Considering the sparse information regarding these resuscitative techniques in veterinary medicine, veterinarians are left with extrapolating information from human trials and experimental animal models.

**Diagnosis** – Viscoelastic tests integrated with predictive scoring systems may prove to be the most reliable methods for early detection of ATC as well as for guiding transfusion requirements.

**Summary** – Hemorrhage accounts for up to 40% of human trauma-related deaths and remains the leading cause of preventable death in human trauma. The exact proportion of trauma-related deaths due to exsanguinations in veterinary patients remains uncertain. Survivability depends upon achieving rapid definitive hemostasis, early attenuation of posttraumatic coagulopathy, and timely restoration of effective circulating volume. Early institution of damage control resuscitation in severely injured patients with uncontrolled hemorrhage has the ability to curtail posttraumatic coagulopathy and the exacerbation of metabolic acidosis and hypothermia and improve survival until definitive hemostasis is achieved.

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**Keywords:** acquired hemostatic defects, blood products, resuscitation, stabilization, surgical hemostasis

## Abbreviations

ATC	acute traumatic coagulopathy
CPP	cerebral perfusion pressure
DCR	damage control resuscitation
DCS	damage control surgery
FCD	functional capillary density
FFP	fresh frozen plasma
FWB	fresh whole blood

Hct	hematocrit
HTS	hypertonic saline solutions
pRBC	packed red blood cells
rhFVIIa	recombinant human factor VIIa
SBP	systolic blood pressure

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## Introduction

Death from massive traumatic hemorrhage may occur within minutes, particularly if a major artery is involved. The primary tenets of hemorrhagic shock resuscitation remain to arrest hemorrhage and restore effective circulating blood volume and tissue perfusion. Secondary goals of resuscitation are to avoid rebleeding and to counter any physiological derangements (eg, coagulopathy, metabolic acidosis, hypothermia) induced

by the traumatic injury, state of shock, or resuscitative intervention. The ability to arrest hemorrhage will in part depend upon the source of its location (eg, extremity versus intracavitary). Bleeding that is inaccessible to immediate, direct hemostasis control can exacerbate the state of shock and lead to death very quickly. The combination of coagulopathy, metabolic acidosis, and hypothermia has been termed the lethal triad of death, which has been associated with a greater mortality rate.<sup>1,2</sup>

Fluid resuscitation has continuously evolved over the past few decades. Traditionally, administering large volumes of non-blood containing fluids (eg, crystalloids and synthetic colloids) has been used to restore lost circulating volume; however, over the past few decades this large-volume approach has been shown to be deleterious in cases of uncontrolled hemorrhage.<sup>3-10</sup> At least for human trauma casualty care, damage control resuscitation (DCR) has been promoted as a more optimal resuscitative approach for the most severely injured patients suffering uncontrolled hemorrhagic shock.<sup>9-13</sup> DCR is described as a rapid, effective resuscitative strategy involving the institution of permissive hypotension or hypotensive resuscitation to allow the restoration of adequate perfusion without disrupting thrombus formation. This approach is based on the use of "hemostatic resuscitation" that involves using whole blood or combined blood product components with very limited crystalloid infusion. The premise of a hemostatic resuscitative approach is to avoid causing iatrogenic hemodilution and exacerbating metabolic acidosis and hypothermia while simultaneously countering any coagulopathy.<sup>9-16</sup> Transfusion strategies have also evolved with more recent evidence from human casualties, which supports the use of warm fresh whole blood (FWB) over blood component therapy when available.<sup>17,18</sup> When FWB is not available then blood products are used in combination using defined ratios of packed red blood cells (pRBC), plasma products, and platelets. Acute traumatic coagulopathy (ATC) is proposed to be manifested by hyperfibrinolysis from massive release of tissue plasminogen activator from the endothelium in conjunction with inhibition of both plasminogen activator inhibitor 1 and thrombin activatable fibrinolytic inhibitor activity caused by enhanced protein C activation. In this regards, antifibrinolytics may also provide a beneficial therapeutic role in the acute trauma setting.<sup>19,20</sup> Unfortunately, prospective randomized clinical trials as well as observational cohort or retrospective studies evaluating the benefits of DCR and hemostatic resuscitation in the veterinary trauma patient is lacking. Therefore, the remainder of this review will cover the main therapeutic interventions for addressing ATC and hemorrhagic shock as extrapolated from human studies and experimental animal models.

### Hemostasis control

Early and prompt hemorrhage attenuation is one of the main priorities of hemorrhagic shock resuscitation. The success of achieving early hemostatic control is often complicated by several factors to include the presence of noncompressible hemorrhage and coagulopathy. Compressible hemorrhage involves extremity wounds that are usually accessible and allow for early hemostasis through direct wound packing, application of hemostatic bandages or agents, or even placement of a temporary tourniquet around a proximal arterial supply. In canine and feline patients, types of compressible hemorrhage involve wounds located on the ears, the thoracic limb distal to the elbow, the pelvic limb distal to the stifle, and the tail.<sup>21,22</sup> Superficial wounds to the thoracic wall, neck, back, upper limbs, and perineum may also fit into the compressible hemorrhage category; however, pending the size and extent of the injury, wounds to these location may only allow for partial compression.<sup>23</sup> For example, placing a circumferential compressive wrap around the neck or thorax may occlude the patient's airway or restrict chest expansion and prevent adequate respiration, respectively. On the other hand, noncompressible wounds are not readily accessible for applying hemostatic control measures as they primarily result from penetrating or blunt injuries to the thorax and torso. Hemorrhage from noncompressible wounds usually result from lacerations or disruptions of major internal vessels or organs that may quickly lead to massive hemorrhage and death. In people, the abdominal cavity, retroperitoneal space, pleural space, gastrointestinal tract, and fascial planes around fractured bones have been identified as anatomical locations where trauma patients can lose enough blood to develop hemorrhagic shock.<sup>20,23-25</sup> One study revealed that 38 of 40 dogs experiencing motor vehicle trauma presented with a hemoperitoneum;<sup>26</sup> therefore, it would be reasonable to consider that these same locations would apply to veterinary trauma patients as well. The initial goals when presented with a trauma patient suffering noncompressible, uncontrollable hemorrhage involve early identification of the bleeding source(s) in conjunction with immediate interventions to minimize further blood loss.<sup>20</sup> At the same time efforts to restore and maintain adequate effective circulatory volume and hemodynamic stability may also be initiated. Optimally, gaining definitive hemostasis for massive, noncompressible hemorrhage would best be served through pursuing early surgical intervention; particularly if the patient has suffered a penetrating abdominal wound or remains hemodynamically unstable despite adequate nonsurgical resuscitative efforts.<sup>20,27-29</sup> In people, life-threatening noncompressible hemorrhage presents a challenge to the first responder as, to date, no prehospital

therapeutic intervention has been definitively proven to be successful in providing prompt hemostatic control.<sup>30,31</sup> Similarly, life-threatening, noncompressible hemorrhage can be challenging for the veterinarian to treat effectively in an emergency situation as well, particularly considering that not all veterinary facilities are well-staffed for emergency surgical intervention or have readily available resources (eg, personnel or blood products) on hand. Fortunately, not all cases involving noncompressible hemorrhage require immediate surgical intervention, and hemostasis can be achieved with medical therapy alone.<sup>32–34</sup>

In both human and veterinary medicine, controversy still surrounds whether immediate surgical versus conservative medical management is the best course of action for addressing traumatic cavitory hemorrhage (eg, hemoperitoneum). The decision will depend upon the clinical assessment of hemodynamic stability, severity of ongoing hemorrhage, the availability of personnel and resources, and, particular to veterinary medicine, financial constraints. In people, a study by Croce et al<sup>35</sup> concluded that nonoperative management of traumatic hemoabdomen involving blunt hepatic injury was safe for hemodynamically stable patients and revealed that there were fewer abdominal complications and fewer transfusions when compared with a matched cohort of patients that underwent surgical intervention.<sup>35</sup> A retrospective study, reviewing 28 cases of traumatic hemoperitoneum in dogs, concluded that medical management did not significantly decrease overall survival, with survival rates of 75% and 67% for animals medically and surgically managed, respectively.<sup>32</sup>

External counterpressure (via application of an “abdominal wrap”) has been shown to provide some therapeutic benefit (both anecdotally and experimentally) in managing traumatic hemoabdomen resulting from blunt trauma in patients assessed to be hemodynamically stable. Pelligra et al<sup>36</sup> demonstrated that application of external abdominal counterpressure, using a pressure of 20–25 mm Hg, for up to 48 hour provided a safe and effective approach for successful abatement of intra-abdominal hemorrhage in people.<sup>36</sup> In a dog model of experimentally induced hemoperitoneum, McAnulty et al<sup>37</sup> demonstrated a greater increase in cardiac index, a slower rate of decline in mean arterial pressure (MAP), attenuation of hemorrhage, and a greater survival advantage in dogs in which abdominal counterpressure was applied compared to those dogs that did not receive abdominal counterpressure.<sup>37</sup> This technique should not be employed if a diaphragmatic hernia is suspected in order to avoid pushing intra-abdominal organs rostrally into the thoracic cavity. Extrapolating from the evidence derived from retrospective studies evaluating human trauma patients and based on current human trauma re-

suscitative guidelines,<sup>20,27–29,38</sup> if intra-abdominal hemorrhage persists or if the patient cannot be hemodynamically stabilized or they relapse back into a state of shock after the application of external counterpressure and institution of DCR, then surgical exploration to achieve direct hemostasis is required to provide the best opportunity for improving early survival. In support of this recommendation, a retrospective analysis of 99 human blunt-trauma patients revealed that casualties failing to respond to initial fluid resuscitative efforts were all hemodynamically unstable and required immediate surgical intervention.<sup>39</sup>

### Traditional fluid resuscitation

Traditionally, resuscitative strategies for countering hemorrhagic shock have focused on replacing extracellular fluid deficits with rapid, large-volume crystalloids to restore normal hemodynamics.<sup>10,40–42</sup> Usually, this approach entailed a 3:1 ratio (sometimes as high as 8:1 for severe shock)<sup>43</sup> of isotonic crystalloid to shed blood instituted prior to definitive hemorrhage control. The “3:1” approach primarily found its origins from controlled hemorrhaged animal models conducted in the 1940s through 1960s by Reynolds, Shires, Canizaro, and others.<sup>44</sup> Using a controlled hemorrhagic canine model, Reynolds discovered increased survival rates were achieved when 1 mL of shed blood was replaced with 2 mL of saline.<sup>44</sup> Later, Shires’ work demonstrated a loss of extracellular fluid volume exceeding the volume of blood loss.<sup>45,46</sup> In addition, they demonstrated a prosurvival effect when the extracellular fluid deficit was rapidly replaced with early institution of a large-volume balanced salt solution (lactated Ringer’s) in a 3:1 replacement fashion.<sup>45,46</sup> During the same time period, Fogelman and Wilson demonstrated that dogs subjected to hemorrhage-induced hypotension experienced lower mortality rates when lactated Ringer’s solution was used in conjunction with shed blood for resuscitation as compared to administering shed blood alone.<sup>47</sup> Although these early experimental studies provided the initial support for large-volume crystalloid resuscitation for hemorrhagic shock, it should be noted that all of these aforementioned experimental studies used a controlled hemorrhage model involving a single source of bleeding. Therefore, their findings may not be applicable to the polytrauma patient suffering hemorrhagic shock from uncontrolled hemorrhage involving multiple bleeding sources. Regardless, the collective findings from these early studies along with ready availability of synthetic fluids contributed to the advent of large-volume isotonic crystalloid resuscitation.<sup>10,14,48,49</sup> Subsequently, the prescribed intervention for prehospital resuscitation of hemorrhagic shock since the Vietnam War has involved the

infusion of large-volume crystalloids in attempt to recoup the blood pressure back to normal as quickly as possible.<sup>10,44</sup> Despite its wide acceptance and clinical implementation, it is interesting to note that no repeatable evidence from randomized clinical trials or retrospective reviews in human or veterinary medicine has ever fully supported this large-volume approach with respect to improving overall survival.<sup>3,50–52</sup>

Over the last few decades, mounting evidence has shown that large-volume crystalloid resuscitation is not innocuous.<sup>4,53</sup> Retrospective analysis and experimental models have shown that large-volume resuscitation may actually exacerbate the hemorrhagic shock-induced inflammatory response, immune dysregulation, and coagulopathy.<sup>4,5,7,53–55</sup> Even despite definitive hemorrhage control, this traditional fluid approach may have contributed to greater overall mortality.<sup>13</sup> Experimental rodent models of trauma and hemorrhagic shock<sup>5,54</sup> have demonstrated that most types of resuscitation regimens (different fluid type and volume administered) cause some degree of increased gut permeability, pulmonary neutrophil sequestration, systemic neutrophil activation, and decreased RBC deformability; a complication referred to as “resuscitative injury.” Interestingly, resuscitation with a 3:1 ratio of isotonic crystalloids (ie, lactated Ringer’s solution) to volume of shed blood provided the most severe morphological and inflammatory changes within the gut and lungs.<sup>5,54</sup>

Evidence from experimental animal models has demonstrated that institution of large-volume crystalloid resuscitation to achieve normotension in situations of acute uncontrolled hemorrhage may worsen hemorrhage, exacerbate blood loss, induce vasoconstrictive dysfunction, and increase mortality<sup>6,53,56</sup> when compared to delayed or hypotensive fluid resuscitative approaches.<sup>4,7,55,57</sup> Investigating a multicompartamental computer model of hemorrhagic shock, Hirshberg et al<sup>58</sup> demonstrated that a 2 L crystalloid bolus administered before intrinsic hemostasis was achieved, increased blood loss from 4% to 29%.<sup>58</sup> Furthermore, that same 2 L crystalloid bolus administered at a high rate (0.2 L/min) did not even transiently correct the existing hypotension in a patient that has lost blood at a rate of 1.5 L in 15 minutes and still has ongoing bleeding. Further, this high volume and rate of crystalloids carried a high probability of triggering rebleeding if administered to a patient during the period when the initial thrombus was forming (usually within the first 30 min of injury). Overall, Hirshberg concluded that administering the standard high rate and volume of crystalloid infusion to a hypotensive patient with ongoing bleeding or during the period of initial thrombus formation provides little benefit, whereby an early bolus delays hemostasis and a late bolus triggers rebleeding.

As mentioned in the accompanying part I of this review,<sup>59</sup> hemodilution via large-volume fluid resuscitation significantly confounds the severity and duration of ATC and in conjunction with acidosis and hypothermia contributes to the phenomenon referred to as “trauma-induced coagulopathy.” Glick et al<sup>60</sup> used a splenectomized, controlled-hemorrhage canine model<sup>60</sup> to evaluate the changes in hematocrit (Hct), prothrombin time, and platelet count induced by large-volume (3:1 lactated Ringer’s solution to shed blood) versus small-volume crystalloid (1:1 lactated Ringer’s solution to shed blood) resuscitation. Acute hemorrhage (30% total estimated blood volume) caused a rapid and moderate drop in mean Hct to 17% below baseline within 15 minutes posthemorrhage. Large-volume fluid resuscitation (3:1) resulted in a further Hct drop to 50% below baseline, whereas small-volume resuscitation (1:1) resulted in a decrease in Hct to only 24% below baseline. In addition, large-volume resuscitation resulted in a more significant prolongation of the prothrombin time and decrease in platelet count as compared to small-volume resuscitation. Interestingly, although large-volume resuscitation resulted in a supranormal elevation of cardiac output initially, this effect was only transient (approximately 30 min) and overall there was no sustained advantage in systemic hemodynamics or end-organ perfusion between the two resuscitative approaches.

Considering less than 20–25% of the infused volume of crystalloids remains within the vasculature and possibly less during states of endothelial injury with increased endothelial permeability,<sup>61</sup> the latter finding from Glick’s study regarding the transient nature of large-volume crystalloid infusion on perfusion seems intuitive. Other studies have shown that in order to maintain hemodynamic stability, large crystalloid volumes are required to be continuously infused at high infusion rates.<sup>62</sup> Although, it has been shown in various animal models that large-volume crystalloids administration may improve hemodynamics in the short term,<sup>62–65</sup> lack of retention in vasculature requiring continued administration of larger volumes to maintain MAP, places the patient at risk for interstitial edema formation, prolonged hemorrhage, and delayed recovery.<sup>4,53</sup>

### **Hypotensive resuscitation/permmissive hypotension**

With mounting evidence exposing the potential adverse effects of large-volume fluid resuscitation, current recommendations and guidelines are trending toward a reduction in prehospital or presurgical fluid volume resuscitation, an approach referred to as hypotensive resuscitation or permmissive hypotension. The premise behind hypotensive resuscitation or permmissive hypotension is to achieve and maintain adequate vital

organ perfusion and tissue oxygenation without further exacerbating blood loss by allowing thrombus formation. The idea and recognition of the potential benefits of hypotensive resuscitation is not a new concept. As early as World War I and II, military physicians had observed an exacerbation of blood loss, elevation in mortality rates, and elevation in transfusion requirements when systolic blood pressure (SBP) was raised above 80–90 mm Hg following the administration of large-volume fluid resuscitation in patients suffering from uncontrolled hemorrhage.<sup>40,41,44</sup> From these observations, physicians were targeting a presurgery SBP of 80–85 mm Hg in patients with truncal injuries and suspected uncontrolled internal bleeding.<sup>41</sup> Subsequently, this early concept of hypotensive resuscitation fell out of favor after Shires and others demonstrated a pro-survival effect with the institution of large-volume resuscitation (3 mL crystalloid for every 1 mL of shed blood) in the 1950s and 1960s.<sup>9,42</sup>

In 1994, Bickell et al<sup>66</sup> was the first to “re-challenge” the traditional approach of early large volume resuscitation by comparing immediate traditional resuscitation versus delayed resuscitation (intravenous catheterization only) in a nonrandomized prospective, clinical trial involving 598 trauma patients admitted with penetrating torso injuries. In this landmark study, patients denied fluids prior to definitive surgical care experienced significantly less intraoperative blood loss, shorter hospital stays, and lower mortality rates as compared to patients treated with the standard large-volume intravenous fluid resuscitation protocol; however, intraoperative transfusion requirements did not differ significantly between groups. It should be noted that the time until surgical care for both delayed and traditionally resuscitated patients was  $\leq 30$  minutes: a facet that may not be feasibly achievable in most veterinary patients.

More recent investigations have demonstrated an improvement in coagulopathy and reduction in hemorrhage volume, hemodilution, acidemia, and cellular injury with subsequent improved survival rates when reduced volumes of prehospital fluids are implemented in hemorrhagic shock resuscitation strategies.<sup>4,53</sup> In 2003, Mapstone et al conducted a systematic review of fluid resuscitation in 44 animal models of hemorrhagic shock.<sup>67</sup> Regardless of the hemorrhage model used (eg, aortic injury, organ incision, tail resection, other vascular injuries), the data collected from Mapstone et al<sup>67</sup> demonstrated that hypotensive resuscitation reduced the risk of death in all trials investigating this strategy. In another retrospective analysis using the German Trauma Registry database and including 17,200 patients suffering from multiple injuries, Maegele et al<sup>68</sup> demonstrated a positive correlation between the incidence of coagulopathy and the amount of prehospital fluids administered,

the greater the volume of prehospital fluids administered resulted in a greater incidence of coagulopathy.<sup>68</sup>

Current trauma resuscitation guidelines have now incorporated hypotensive resuscitation in select subsets of trauma patients. The American Heart Association 2005 Guidelines for Cardiopulmonary Resuscitation and Emergency Care states<sup>69</sup> that “aggressive prehospital volume resuscitation for penetrating trauma is no longer recommended because it is likely to increase blood pressure and consequently accelerate the rate of blood loss, delay arrival at the trauma center, and delay surgical intervention to repair or ligate bleeding vessels. . . . In rural settings, transport times to trauma centers will be longer, so volume resuscitation for blunt or penetrating trauma is provided during transport to maintain a systolic blood pressure of 90 mm Hg.” The exception the guidelines make is for casualties suffering isolated head injury where the recommendation is to provide volume resuscitation in order to maintain a SBP  $\geq 100$  mm Hg. Similarly, starting in 2008 the Advanced Trauma Life Support guidelines<sup>70</sup> advocate a “balanced” fluid resuscitation approach. A strategy that accepts a certain degree of hypotension in order to balance the primary goal of organ perfusion against the risks of rebleeding that may develop with resuscitation to a normotensive state. The ATLS guidelines further state that “hypotensive” or “permissive hypotensive” resuscitation may serve a role in patients with uncontrolled hemorrhage. However, it precedes that statement with the concept of using a “balanced” fluid resuscitative approach with frequent evaluations of perfusion, and that delayed resuscitation is not an alternative for definitive surgical control of bleeding.

At least one meta-analysis evaluating hypotensive resuscitation did not show any advantage over traditional fluid resuscitation strategies.<sup>71</sup> In addition, evidence from several other studies evaluating hypotensive resuscitation during uncontrolled hemorrhage has demonstrated that the most favorable results are expected when definitive hemostasis is achieved within a short period of time.<sup>39,50,53,72,73</sup> The concept of withholding fluids completely until definitive surgical control of hemostasis (delayed resuscitation) has also been evaluated. Although, some studies have shown a benefit,<sup>66,74</sup> several other studies have shown a more detrimental outcome when instituting a delayed fluid approach;<sup>75,76</sup> however, transport times from the site of injury to the trauma center play a significant role in outcome. In cases of short transport times (ie,  $<20$ – $30$  min), the “scoop and run” technique in which prehospital interventions (eg, catheter placement, fluid administration) are avoided in attempts to hasten transport to the hospital has been shown to improve survival in a small proportion of trauma patients.<sup>77,78</sup>

### Optimal blood pressure target for controlled hypotensive resuscitation

Several experimental studies have shown that maintaining an SBP of approximately 90 mm Hg and an MAP around 60 mm Hg, until definitive surgical hemostasis was achieved, resulted in increased oxygen delivery, decreased blood loss, and reduced mortality.<sup>7,56,79–82</sup> Sondeen et al<sup>82</sup> demonstrated in swine that an MAP of  $64 \pm 2$  mm Hg and an SBP of  $94 \pm 3$  mm Hg were the average reproducible pressures at which rebleeding occurred and further concluded that these should be considered as the pressure values to target during uncontrolled hemorrhage resuscitation. In another swine model, Stern et al<sup>80</sup> demonstrated that intraperitoneal bleeding and mortality were significantly greater while mean survival time was significantly shorter in animals resuscitated to an MAP of 80 mm Hg as compared to animals resuscitated to an MAP of 40 or 60 mm Hg; furthermore, the 60 mm Hg group demonstrated a significantly greater oxygen delivery as compared with the other 2 groups. Using a controlled canine hemorrhage model, Friedman et al<sup>83</sup> evaluated blood pressure targeted fluid resuscitation by infusing either lactated Ringer's solution to a targeted MAP of 60 or 80 mm Hg versus hydroxyethyl starch solution to an MAP of 60 mm Hg.<sup>83</sup> Not surprisingly, the group resuscitated with lactated Ringer's solution to a targeted MAP of 80 mm Hg required the greatest volume of fluid to achieve and maintain the targeted MAP as well as resulted in the greatest volume of blood loss. The group resuscitated with hydroxyethyl starch solution to a targeted MAP of 60 mm Hg required the least amount of fluid to achieve the targeted MAP, resulted in the smallest amount of blood loss, and also resulted in better overall oxygen delivery and improvement in lactate concentration.

A couple of important questions to consider relative to this topic are: (1) what is the lowest blood pressure that can be sustained? and (2) how long can this blood pressure be maintained before it becomes more deleterious than beneficial? A few experimental animal models have provided us with a little insight into these concerns. Following a 72-hour observation period, Stern et al<sup>84</sup> observed no significant histological or physiological evidence of end-organ injury (eg, liver, kidney, pulmonary, neurologic) after subjecting swine to 75 minutes of under-resuscitation (MAP of 40 mm Hg); however, they noted that achieving an MAP of approximately 60 mm Hg resulted in better maintenance of tissue perfusion and greater trend toward survival. After subjecting rats to an MAP of 40 mm Hg for 60 minutes or an MAP of 30 mm Hg for 45 minutes and then resuscitating both groups of rats with either citrated shed blood or lactated Ringer's solution, Carrillo et al<sup>85</sup> did not observe any significant functional or histologic neurological damage.<sup>85</sup>

In a rodent hemorrhagic shock model,<sup>86</sup> Li demonstrated that an MAP of 50–60 mm Hg for up to 90 minutes resulted in significantly better hemodynamics and overall survival as compared to animals in which the MAP was maintained <50 mm Hg or >60 mm Hg or in animals exposed to an MAP of 50 mm Hg for >90 minutes.

How long can permissive hypotension be maintained before it causes more detriment than benefit? As early as the 1950s, Carl Wiggers demonstrated in a canine hemorrhage model that a state of "irreversible" shock from hemorrhage was at greatest risk only after experiencing several hours (eg, >3–4 h) of sustained moderate hypotension (MAP approximately 50–60 mm Hg) or after sustaining a brief period (45 min) of severe hypotension (MAP approximately 30–40 mm Hg).<sup>87</sup> In a porcine model of controlled hemorrhagic shock, Skarda demonstrated that patients subject to a pressure-targeted resuscitation with a SBP = 65 mm Hg for 8 hours experienced a greater decrease in tissue oxygen saturation (StO<sub>2</sub>) and greater mortality rate as compared to those resuscitated to a target SBP of 80–90 mm Hg.<sup>88</sup> A recent study by Garner et al<sup>89</sup> demonstrated that an SBP targeted to 80 mm Hg for 8 hours was not compatible with survival in a porcine model of controlled hemorrhage and primary air-blast injury (received from a remotely detonated explosive charge).<sup>89</sup> Interestingly, 100% (8/8) of the animals hemorrhaged without blast injury and resuscitated to SBP of 110 mm Hg survived to the end of the 8-hour study, whereas only approximately 62% (5/8) of animals hemorrhaged without blast injury and administered hypotensive resuscitation to an SBP of 80 mm Hg survived. Similarly, approximately 67% (4/6) of the animals suffering both hemorrhage and blast injury and receiving normotensive resuscitation survived for the full 8 hours after the onset of resuscitation, whereas none (0/6) of the same subset of animals administered hypotensive resuscitation survived beyond 209 minutes. An important concept that can be interpreted from Wiggers, Skarda, and Garner's research is that there is a definite clinical and prognostic distinction between simply the presence of hemorrhage-induced hypotension and the onset of irreversible hemorrhagic shock. If left untreated for several hours, it seems evident that hemorrhage-induced hypotension can progress into irreversible hemorrhagic shock resulting in end-organ damage and mortality. But if addressed appropriately and in a timely fashion, the progression of hemorrhage-induced hypotension into irreversible hemorrhagic shock may be abated. Overall, the evidence from these few experimental animal models would suggest that brief periods (60–90 min) of permissive hypotension (MAP approximately 50–60 mm Hg or SBP 80–90) does not significantly increase the risk of irreversible end-organ damage or mortality. However, hypotension sustained at lower values (<50 mm Hg) or

for longer periods of time can be more detrimental than beneficial. These findings are in alignment with data and recommendations based off other experimental animal models and human retrospective studies that demonstrated hypotensive resuscitation during uncontrolled hemorrhage provides the most favorable results when definitive hemostasis is achieved within a short period of time.<sup>39,50,53,73</sup>

### Controlled hypotensive resuscitation and head injury

Contraindications to a delayed or hypotensive resuscitative approach may involve traumatic brain and spinal cord injuries where maintaining adequate cerebral perfusion pressure (CPP) to the neuronal tissues is vital for recovery. Some studies have implicated that traumatic brain injury coupled with hypotension contributes to significantly increased mortality rates;<sup>90</sup> therefore, it may seem reasonable that rapid restoration of CPP is necessary for optimal neurological recovery. Considering CPP is dependent upon MAP ( $CPP = MAP - \text{Intracranial pressure}$ ), under-resuscitation with a delayed or hypotensive approach may result in decreased CPP with development of subsequent secondary brain injury.<sup>64</sup> However, a few experimental studies have shown no adverse affect on cerebrovascular hemodynamics with delayed fluid resuscitation.<sup>91,92</sup> Interestingly, analysis of data collected from the National Trauma Data Bank from 1994 to 2001 identified hypotension as an independent risk factor for mortality that did not influence mortality rates between patients with or without traumatic brain injury.<sup>92</sup> Adequate clinical evidence is lacking regarding the appropriate resuscitative strategy for combat casualties with traumatic brain injury. Moreover, there is a lack of definitive knowledge regarding the association of concurrent hypotension and traumatic brain injury on mortality. Recognizing the lack of data to support a standard resuscitative strategy, the 2005 Brain Trauma Foundation Guidelines for Field Management of Combat-Related Head Trauma do not currently advise permissive hypotensive resuscitation for combat casualties suffering traumatic brain injury, but do recommend hypertonic saline as the initial resuscitative fluid of choice.<sup>93</sup>

### DCR

Between 1998 and 2001, the Office of Naval Research along with other federal and international organizations (ie, Institute of Medicine) issued 3 different consensus statements including recommendations for the optimal resuscitation protocol for the combat casualty.<sup>10</sup> Analysis from all 3 consensus conferences concurred that large volume fluid resuscitation was harmful, therefore, recommendations were made favoring a more controlled hypotensive resuscitative strategy in casualties with un-

controlled hemorrhage. Following the Office of Naval Research's consensus recommendations, the US Military Committee on Tactical Combat Casualty Care decided to implement the "permissive hypotensive" approach into their resuscitative strategy.<sup>94</sup>

Military combat physicians and urban trauma surgeons have realized that early prevention and reversal of the lethal triad (ie, hypothermia, metabolic acidosis, and coagulopathy) is paramount for increasing survivability in trauma casualties. The high volume of combat casualties sustained from ongoing military conflicts along with the logistical dilemma of maintaining readily available blood products on the battlefield has favored the institution of DCR, a proactive strategy most applicable to those casualties suffering from severe hemorrhagic shock with ongoing uncontrolled bleeding and concurrent coagulopathy.<sup>11</sup> DCR is a resuscitative approach designed to systematically and rapidly (within the initial 24–48 h) reverse hypothermia, acidosis, and coagulopathy<sup>95,96</sup> and, therefore, "optimize" the patient before pursuing definitive resuscitation or surgical repair. The main advantage of DCR lies in its ability to provide the physician with an effective therapeutic approach for abating or minimizing the immediate adverse effects exerted by hemorrhagic shock while also being challenged with lack of readily available personnel and logistical resources. DCR involves direct treatment of coagulation abnormalities with appropriate ratios of blood component products; limited fluid resuscitation to maintain an SBP of approximately 80–90 mm Hg until major hemorrhage has been halted, early prevention and correction of hypothermia, utilization of whole blood and blood products as the primary source of volume resuscitation (hemostatic resuscitation), and abolishment of excessive use of isotonic crystalloids.

In human trauma patients presenting with life-threatening, noncompressible hemorrhage or that are in overt shock, the resuscitative recommendation that is now gaining popularity involves titrating appropriate blood product components (if available) or hypertonic saline combined with a synthetic colloid in small 250–500 mL aliquots until mental status improves (in absence of significant head injury) and an SBP of approximately 80 mm Hg or MAP of approximately 60 mm Hg is achieved.<sup>61</sup> In veterinary patients, 2–6 mL/kg aliquots of 7.5% hypertonic saline combined with synthetic colloid has been recommended for shock resuscitation.<sup>97</sup> If traumatic brain injury is suspected, then the recommendation is to maintain the SBP at 90 mm Hg or greater.<sup>10,93,94</sup> When blood pressure measurement devices are not logistically attainable (eg, battlefield trauma) or readily available, then improvement in mental status and acquisition of a radial pulse have been cited as useful "field" parameters for assessing perfusion in human trauma

patients.<sup>1,10,70,74</sup> In theory, a palpable radial pulse in people should correspond to an SBP of approximately 80–85 mm Hg,<sup>12,74</sup> which in the veterinary patient could potentially equate to achieving a palpable dorsal pedal pulse. It is worth remembering that the palpable pulse pressure simply reflects that difference between systolic and diastolic arterial pulse pressures, and although cited frequently, the evidence supporting the use of a palpable pulse to predict an actual blood pressure value is lacking.<sup>1,10,70,74,98,99</sup> A study evaluating the relation between a palpable carotid, femoral, and radial pulse in hypotensive human patients found that the acquisition of peripheral pulses correlated with an SBP that were actually below the much cited value of 80–85 mm Hg.<sup>98</sup> Due to the inherent variability in physiologic responses between patients as well as the examiners' ability to palpate and assess the pulse quality, the direct relation between a palpable pulse and actual SBP or MAP value can be highly subjective and unreliable. In essence, the absence of a palpable dorsal pedal pulse in a dog or cat does not always mean the SBP is below 80 mm Hg, whereas its presence does not always ensure an SBP  $\geq$  80 mm Hg. In human combat casualty care, the use of a palpable radial pulse as an indicator of adequate blood pressure is primarily reserved for field situations when no blood pressure device is readily available.<sup>1,9,94,100</sup> Similarly, improvement in mentation along with acquisition of a dorsal pedal or femoral pulse may serve as a useful resuscitative guide in veterinary patients in situations when blood pressure devices are not readily available.

With severe exsanguination, transfusion of whole blood or blood products is required for restoring oxygen delivery to tissues and coagulation. In DCR, restoration of circulating blood volume is delayed until definitive control of hemorrhage is obtained, at which time FWB or an appropriate combined ratio of blood components are used to restore hemodynamic parameters, a strategy referred to as "hemostatic resuscitation."<sup>101</sup> Transfusion recommendations have continually evolved over the past century from the use of whole blood to modified blood components to nonblood component fluids (eg, crystalloids and synthetic colloids) to the current use of stored blood component therapy in conjunction with crystalloids or synthetic colloids. The type and amount of blood products used for resuscitation still remains controversial with no standardized algorithmic guideline in place to assist clinicians. Despite the lack of evidence supporting its improvement in survival, blood component therapy has prevailed as the primary therapeutic choice for replacing human trauma victims' lost blood volume.<sup>14</sup> Retrospective data from ongoing combat operations in Afghanistan and Iraq may suggest a potential advantage of using warm FWB over stored blood

products or synthetic fluids (eg, crystalloids and colloids) as the primary resuscitative fluid for hemorrhagic shock.<sup>9,18,102,103</sup> Similarly in a comparison study, dogs experiencing hemorrhagic shock were resuscitated with one of the following strategies: autologous shed blood, normal saline, Hespan, Oxyglobin, or vasopressin. Although, all fluid strategies improved systemic hemodynamic function, shed blood was the only strategy that returned the parameters back to normal baseline values.<sup>104</sup> While stored blood products provide a logistical advantage and allow for correction of specific hemostatic deficiencies, they have not been shown to consistently increase tissue oxygenation or even improve survival.<sup>105</sup> In fact, the regulatory standard for stored RBCs only mandates that 75–80% of the transfused RBCs remain in circulation during the first 24 hours posttransfusion, the mandate makes no stipulation on the ability of the remaining transfused RBCs to adequately transport or deliver oxygen to the microvasculature or tissues.<sup>102</sup> One reason for the lack of stored RBCs to adequately deliver and offload oxygen to cells and tissues is related to low concentrations of 2,3-diphosphoglycerate, causing an increase in oxygen affinity or binding to hemoglobin, a known storage lesion of RBCs.<sup>102</sup> Another reason is due to impairment of microcirculatory flow from hemorheological alterations, such as increased osmotic fragility, altered RBC shape, decreased RBC membrane deformability, and increased RBC membrane loss that occurs during storage. Particularly when compared to similar volume transfusions with FWB, the number of capillaries that possess transiting RBCs per unit volume of tissue or the functional capillary density (FCD) becomes significantly decreased with transfusion of stored products, a complication that also occurs with resuscitation using crystalloids and colloids.<sup>17,106</sup> Depending upon the volume, number of units transfused, and length of storage, the stored blood products have been associated with increased mortality and morbidity. In addition, the administration of component blood products may also pose a greater risk of exacerbating any present anemia, thrombocytopenia, or coagulopathy as compared to FWB.<sup>18</sup> In brief, storage lesions induce proinflammatory and immunosuppressive effects, decrease oxygen transport capabilities of RBCs, and diminish FCD and microvascular flow – complications that can be mitigated with transfusion of FWB.<sup>105</sup> Nonetheless, even though stored RBC products diminish microvascular flow, they actually exert a more favorable effect on FCD as compared to resuscitation with crystalloids or colloids.<sup>17</sup> Overall, even if prospective randomized clinical trials supports the evidence that FWB is the most efficacious resuscitative fluid, its use will still be limited by its lack of ready availability; therefore, blood product component



therapy still remains a primary resuscitative resource for human trauma-induced hemorrhagic shock.<sup>9,18</sup>

A resuscitative strategy not commonly cited in the literature for human trauma patients is the use of autotransfusion (autologous transfusion) or the collection and reinfusion of the patient's own blood. This can be a lifesaving technique for patients experiencing significant closed cavity hemorrhage (eg, thoracic or abdominal cavity), particularly when FWB or stored blood products are not immediately available. Other major advantages of an autologous compared to an allogenic blood transfusion include blood compatibility, decreased transfusion-related events, and lack of infectious disease transmission. Depending upon the size of the patient, blood may be collected aseptically into a sterile syringe or sterile container/commercially prepared transfusion collection bag. Blood collected from chronic hemorrhage (eg, >24 h) into a body cavity that has come into contact with serosal surfaces technically should not be used due to the presence of proinflammatory mediators and microaggregates of leukocytes and RBC lysis that may precipitate a systemic inflammatory reaction and potentially disseminated intravascular coagulation; however, in life-threatening situations the benefit of immediate oxygen carrying support may outweigh the risk when no other blood product is immediately available. In general, blood that has come into contact with serosal surfaces for more than an hour starts to become defibrinated, and in most cases of chronic hemorrhage the blood most likely can be collected and transfused without adding an anticoagulant. For more acute hemorrhages, anticoagulation of collected blood is necessary. As with any transfusion, autotransfused blood should always be administered through either a blood administration set or in-line blood filter. Complications associated with autotransfusions may include hemolysis, bacterial contamination, coagulopathy, thrombocytopenia, microembolism, and potential dissemination of ingesta, fecal material, or urine if intra-abdominal trauma has caused rupture of the bowels or bladder. The current human recommendations for hemostatic resuscitation is to target a hemoglobin between 7 and 9 mg/dL and a platelet count above  $50 \times 10^9/L$  or above  $100 \times 10^9/L$  with concurrent severe head injury.<sup>107</sup> Cryoprecipitate should be considered if fibrinogen concentrations are <100–150 mg/dL or when viscoelastic tracings (thromboelastography or rotational thromboelastometry) suggest low fibrinogen concentrations.<sup>1,9,107</sup> As an acceptable substitute for whole blood in deterring a dilutional coagulopathy and countering a potential consumptive coagulopathy, some advocate administering blood component therapy at a combined 1:1:1 ratio of pRBC: fresh frozen plasma (FFP):platelets.<sup>1,9,107</sup> Evidence from other studies<sup>101</sup> has not supported the combined 1:1:1 ap-

proach, but has instead demonstrated increased survival when implementing a less aggressive FFP:pRBC (1:2 to 1:3) and platelet:pRBC (1:5) transfusion protocol.<sup>15,101,108</sup> Although some studies have shown improved survival with early administration of high FFP:pRBC ratios, other studies have shown no advantage at all.<sup>107</sup> Interestingly, supporters of the enhanced activated protein C pathway hypothesis have even contended that FFP may actually potentiate ATC by supplying more substrates for thrombin formation.<sup>9</sup> It remains evident that definitive evidence from prospective randomized control studies are needed to solve the controversy, thereby, allowing clinicians to make a better informed decision on the optimal blood product ratio. Currently, there are no defined or agreed upon veterinary therapeutic guidelines or recommendations available for addressing trauma-related hemorrhagic shock; therefore, therapeutic intervention in veterinary medicine is mainly extrapolated from human medicine.

Human patients suffering hemorrhagic shock that also experience ATC most often require a massive transfusion.<sup>14</sup> A massive transfusion is generally defined as the transfusion of whole blood or blood components at a volume that is greater than the patient's estimated blood volume within a 24-hour period, half of the patient's estimated blood volume in 3 hours, or the replacement of 150% of the patient's blood volume irrespective of time.<sup>109</sup> In people, a massive transfusion is more commonly defined as transfusion of 10 or more units of RBCs within a 24-hour period.<sup>14,110</sup> In human trauma cases, it has been shown that any delay in instituting a massive transfusion when it was needed has been associated with increased mortality.<sup>14</sup> In order to identify those casualties requiring a massive transfusion early, predictive scoring systems using clinical variables (mechanism of injury, heart rate, blood pressure) with point-of-care and laboratory tests (eg, lactate, base deficit, hemoglobin concentrations, activated partial thromboplastin time/PT or viscoelastic tests [rotational thromboelastometry or thromboelastography], focused assessment with sonography in trauma) have been instituted at human trauma centers.<sup>14,110</sup> Further, massive transfusion protocols have been developed and implemented to guide the transfusion of pRBC, plasma, and platelets in predetermined and standardized ratios to curtail the misuse or unnecessary use of massive transfusions. Predictive scoring systems as well as the exact massive transfusion protocol vary from hospital to hospital.<sup>110</sup> Interestingly, regardless of the combined blood product ratio used in a massive transfusion protocol, current evidence has shown that consistent implementation and adherence of a standardized massive transfusion protocol leads to a reduction in blood component use and multiple organ failure as well as an improvement in

overall outcome.<sup>9,10,101</sup> A retrospective analysis of 15 dogs<sup>109</sup> demonstrated that massive transfusions can be used successfully to manage marked anemia for various reasons (eg, acute blood loss, hemolysis, coagulopathy). The two main abnormalities noted in all dogs included low ionized calcium and progressive thrombocytopenia. Prolongation in the activated partial thromboplastin time and PT was observed in 3 of 15 dogs, while adverse transfusion reactions (eg, transient fever, vomiting, facial swelling, and delayed hemolysis) were reported in 6 of 15 dogs. Only 4 dogs survived to discharge in which the authors surmised that the high mortality rate was more likely the result of the underlying disease process rather than from adverse effects or complications of the massive transfusion. It was further noted that due to the limited number of survivors it was difficult to draw any absolute conclusions regarding relative risk factors associated with massive transfusions in dogs.

In conclusion, retrospective analyses have revealed a survival benefit with implementation of DCR when compared to patients treated with a more traditional resuscitative approach.<sup>2,13,15</sup> In fact in the current Iraq and Afghanistan conflicts, implementation of a damage control strategy has significantly reduced the battlefield mortality rate from the historic 18–20% to a low of 10–12%.<sup>16</sup> Unfortunately, due to lack of evidence from prospective randomized clinical trials supporting the advantage of DCR over traditional resuscitative strategies, the effectiveness of DCR has come under scrutiny by some.<sup>9,111</sup> Even Bickell's 1994 study was not completely supportive. For example, if the investigators would have included patients that died prior to evacuation in their overall analysis, they would have shown no survival advantage in delaying fluid resuscitation. In addition, the applicability of their results to casualties suffering blunt trauma or experiencing a longer duration until definitive surgical care is questionable, particularly, since a subgroup analysis on the patient data from Bickell's 1994 study found that only patients with a penetrating heart injury that also received delayed fluid resuscitation experienced a survival advantage.<sup>9,112</sup> Until further evidence from prospective randomized clinical trials demonstrate a definitive advantage of DCR over traditional fluid resuscitative strategies, the optimal resuscitative approach still remains in question.

### Damage control surgery

Damage control surgery (DCS) is an abbreviated surgical intervention for achieving rapid initial control of hemorrhage and contamination while attempting to reduce the exacerbating effects of acidosis and hypothermia.<sup>113</sup> Considering that body heat may be lost at a rate of approximately 4–5°C/h during a laparotomy and that irre-

versible injury from hypothermia may occur after only 60–90 minutes, an expedited surgical procedure (<1 h) intuitively provides a survival advantage.<sup>9</sup> DCS involves a 3-tiered approach: initial abbreviated surgery to control hemorrhage, intensive care to correct physiological derangements (eg, acidosis, hypothermia, coagulopathy), and finally, definitive surgical repair of injuries. For example, DCS may only entail a brief laparotomy with intra-abdominal packing and temporary closure, if the source of hemorrhage is not readily found, followed by a subsequent re-exploration for definitive repair 24–72 hours later after the patient has been adequately resuscitated while in the intensive care unit. Basically, DCS follows the “get in and get out” theory, where most would recommend keeping surgical time to <1 hour. Reported complications of DCS include abdominal compartment syndrome, sepsis, and multiple organ dysfunction syndrome.<sup>113</sup> DCR and DCS are not separate entities but should be incorporated together in a “damage control strategy.”

### Nonsanguineous Fluid Resuscitation

The topic relating to the optimal resuscitative fluid type (ie, crystalloid versus colloid) also remains controversial. Interestingly though, to date, there is no absolute evidence from randomized clinical trials in human or veterinary medicine showing that one fluid type is superior to another for improving overall survival.<sup>114–116</sup> In fact, there is also no clinical trial demonstrating that one isotonic crystalloid is superior to another;<sup>114–116</sup> although, lactated Ringer's solution composed of the L-lactate isomer only has been shown to exert less adverse immunoinflammatory effects as compared to the racemic (D- and L-isomer) lactated Ringer's solution and normal physiological saline.<sup>10</sup>

Controversy and confounding evidence also still surrounds the “crystalloid versus colloid” debate.<sup>115–118</sup> As compared to isotonic crystalloids, nonprotein colloids (ie, hydroxyethyl starches, dextrans, gelatins) can increase and sustain vascular volume with significantly smaller volumes of infusion. They achieve this primarily due to their enhanced oncotic property that allows them to remain within the vasculature for a prolonged period of time.<sup>62,116</sup> Other proposed benefits include reduction in capillary leak and gut interstitial edema formation, as well as greater improvement in microcirculatory perfusion and oxygenation to the skin and splanchnic microcirculation.<sup>115,116</sup> Unfortunately when outcome is used as the primary endpoint, meta-analyses have failed to provide adequate enough evidence to indicate that colloids are better than crystalloids for resuscitation.<sup>48,115–118</sup> Some meta-analyses have even concluded that colloids may be associated with increased

mortality.<sup>117,118</sup> In addition, the use of synthetic colloids has been implicated with several adverse events to include a dose-related coagulopathy and platelet dysfunction, exacerbation of the proinflammatory response, and induction of acute renal injury.<sup>119–125</sup>

Hypertonic saline solutions (HTS) have also made a re-emergence into the trauma resuscitation world.<sup>10,97</sup> Unlike isotonic crystalloids, experimental animal models have shown HTS may exert positive immunomodulatory effects primarily attributable to alterations of neutrophil-endothelial interactions.<sup>10,126–131</sup> Other reported benefits of HTS include reduced endothelial cell swelling, improved regional blood flow and microcirculation, improved cardiovascular function, and reduced edema formation due to less overall fluid requirements.<sup>10,97</sup> With the mounting evidence that large-volume fluid resuscitation may cause more harm than benefit, one of the main advantages of using HTS over isotonic crystalloids is that significantly smaller volumes of infusion (4–6 mL/kg) are needed to expand the intravascular volume and improve cardiovascular function.<sup>62,97</sup> However similar to crystalloids and colloids, the use of HTS does not come without risks, and prospective clinical trials supporting HTS' absolute superiority over isotonic crystalloid resuscitation as well as its absolute proven benefits for trauma resuscitation are currently lacking. Some experimental animal models have shown that the rapid rise in MAP following HTS infusion can exacerbate bleeding and increase mortality in situations involving uncontrolled, noncompressible hemorrhage.<sup>6,10,97,132,133</sup> In addition, a recent randomized clinical trial comparing shock resuscitation with hypertonic saline versus normal 0.9% saline was halted due to lack of 28-day survival benefit in the hypertonic saline group. Interestingly, victims treated with hypertonic saline were more likely to die in the prehospital phase, while people treated with normal saline suffered a greater mortality rate during the remainder of the 28-day observation period.<sup>134</sup>

HTS combined with a nonprotein colloid have also been evaluated in experimental animal models for shock resuscitation.<sup>10,135–140</sup> Considering the intravascular volume, expanding effects of HTS are transient in nature, combining it with a synthetic colloid can significantly prolong its hemodynamic effects.<sup>97,116</sup> In experimental animal models, the HTS-colloid combination has been shown to provide greater restoration of hemodynamic and microvascular parameters with the least detrimental effect on exacerbating bleeding or hemorrhage-induced inflammation and immunomodulation as compared to when isotonic crystalloids, hypertonic saline, or synthetic colloid infusion are administered alone.<sup>10,135–140</sup> However, similar to the debate between crystalloids versus colloids, the benefits of combining HTS with a non-

protein colloid have not been shown to be absolute. At least 2 controlled canine hemorrhagic shock models demonstrated that small infusions (approximately 4–6 mL/kg) of HTS-colloid solutions were significantly inferior to both lactated Ringer's (administered in a 3:1 ratio to shed blood) and 200/0.5 and 130/0.4 hydroxyethyl starch solutions (administered in a 1:1 ratio of shed blood) in their ability to improve systemic and regional tissue oxygenation.<sup>141,142</sup>

A more in-depth discussion comparing the properties of each fluid as well as the advantages and disadvantages between the different fluid types (eg, crystalloids, colloids, and HTS) is beyond the scope of this article. In summary, considering the conflicting results from different studies, absolute evidence supporting any one fluid as the ultimate resuscitative fluid is still controversial and lacking.

### Pharmacological adjuncts

Pharmacological agents have been and are currently under investigation as adjunctive therapy to blood transfusions for treating hemorrhagic shock in human trauma patients. Most notable is recombinant human factor VIIa (rhFVIIa) concentrate that as a procoagulant promotes formation of the fibrin plug via activation of factor X. Although it appears rhFVIIa may provide some advantage for reducing transfusion requirements in blunt trauma patients, evidence supporting its benefits for overall outcome as well as use in penetrating trauma is conflicting.<sup>9,96,143,144</sup> As with FFP usage in ATC, theoretically rhFVIIa may actually exacerbate ATC by providing the necessary substrate to promote increased thrombin formation and accelerate the thrombomodulin-thrombin activated protein C pathway and subsequent hypocoagulopathy. Considering acidosis and hypothermia can significantly decrease serine protease function, it is intuitive that rhFVIIa may be most applicable in a fully resuscitated patient as compared to the under-resuscitated patient.<sup>95</sup> Current human guidelines recommend not using rhFVIIa as a first line therapy, but rather, to consider rhFVIIa to achieve hemostasis for ongoing hemorrhage that is refractory to traditional efforts and after reaching the following endpoints with the administration of blood products: Hct > 24%, hemoglobin 7–9 mg/dL, pH > 7.2, platelets >  $50 \times 10^9$ , and fibrinogen > 1 g/L.<sup>9,101</sup> Although shown to be effective at correcting hemostatic defects in dogs with hemophilia A and B, the limitations of cost and high-antigen response account for why rhFVIIa is not currently available or clinically feasible for use in veterinary medicine.<sup>145</sup> Recently, a pilot study demonstrated that a single dose of recombinant canine FVIIa was safe to administer and efficacious in correcting hemophilic coagulopathy when administered to a

hemophilic A dog and a hemostatically normal dog.<sup>146</sup> Further studies will need to be conducted to evaluate its clinical utility.

With hyperfibrinolysis contributing to the pathophysiology of ATC, antifibrinolytics may have a role in the early posttraumatic resuscitative period. Tranexamic acid and  $\epsilon$ -aminocaproic acid are the two synthetic lysine analogues that have been proven beneficial for controlling hemorrhage in human cardiovascular surgery and, therefore, have been proposed for use in ATC. In 2010, the clinical randomization of an antifibrinolytic in significant hemorrhage trial<sup>147</sup> showed that tranexamic acid administered postinjury to human trauma patients, suffering either penetrating or blunt injuries, significantly reduced the risk of death due to bleeding without significantly increasing vascular occlusive events (eg, myocardial infarction, pulmonary embolism, stroke); however, it did not significantly reduce transfusion requirements.<sup>148</sup> A follow-up analysis further revealed that tranexamic acid was most effective when administered within 3 hours postinjury regardless of patient's SBP or type of injury (penetrating versus blunt).<sup>19</sup> Aminocaproic acid is significantly less potent (approximately 10-fold) and has a relatively shorter half-life (60–75 min) as compared to tranexamic acid (approximately 120 min);<sup>20</sup> therefore, it is required to be administered as a constant rate infusion (15 mg/kg/h). To the authors' knowledge, no prospective clinical or experimental studies evaluating the use of aminocaproic acid for treating trauma-related hemorrhage are currently available in human or veterinary medicine. Although an increased thrombotic risk is a potential concern with the use of antifibrinolytics, a recent meta-analysis of their use in human patients did not support this concern.<sup>20</sup> Current human guidelines support the use of antifibrinolytics during the acute stages of trauma-related hemorrhage; however, it is further recommended that viscoelastic analysis guide their usage.<sup>107,148</sup> More recently, investigators from the Koret School of Veterinary Medicine in Israel presented an abstract describing the use of tranexamic acid in 68 dogs with various bleeding disorders.<sup>149</sup> This was a retrospective analysis where the authors concluded that although tranexamic acid appeared safe to use clinically in dogs that it did not appear to reduce transfusion requirements as compared to control dogs. Another abstract by Blackstock et al<sup>150</sup> revealed that as compared to the reported therapeutic plasma concentrations in people, dogs may require higher doses of tranexamic acid and aminocaproic acid to achieve similar antifibrinolytic effects.<sup>150</sup>

Other agents (eg, desmopressin, antithrombin) have not shown any clinical benefit in regards to ameliorat-

ing ATC in people or experimental animal models and, therefore, are not currently recommended.<sup>20</sup> It must be emphasized that pharmacological interventions should not constitute the sole method for achieving hemostasis, but only serve as an adjunct to more traditional direct measures for achieving hemostasis (eg, wound packing, surgical ligation).

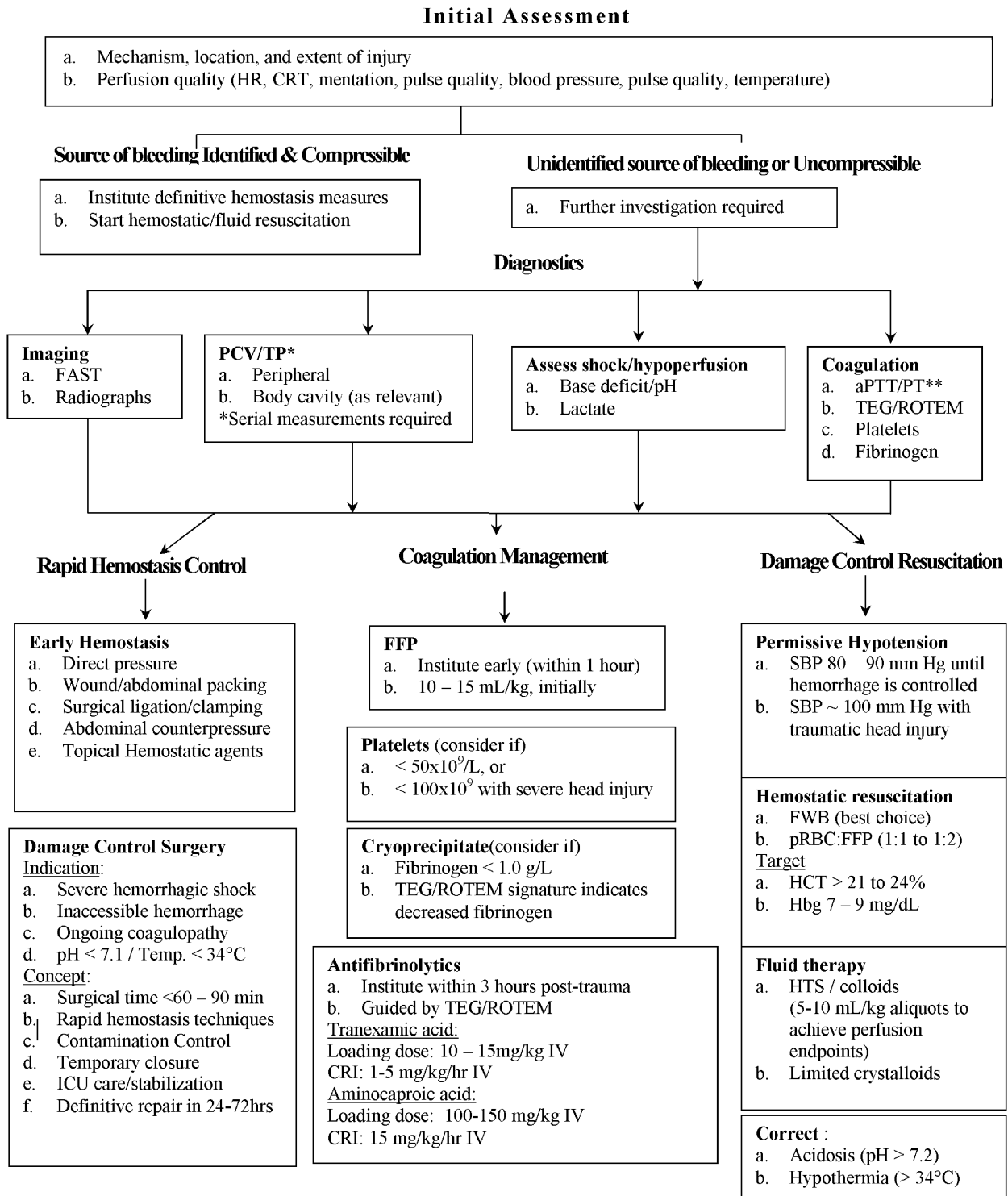
### **Veterinary Application**

As already stated, no standard guidelines are available for directing trauma resuscitation in veterinary patients, nor is there any consensus in veterinary medicine on the prevalence or how to identify ATC in veterinary trauma patients. Due to these limitations, the authors' current suggestions for addressing ATC in veterinary patients are based off supporting evidence extrapolated from human literature and experimental animal data related to this topic. Tables 1, 2 and 3 provide an overview and reasonable guidelines for addressing patients presenting with acute traumatic (penetrating and blunt) injuries with concurrent uncontrolled hemorrhage and ATC. Figure 1 provides an algorithmic approach to ATC.

### **Summary**

Current therapy is empiric in nature, but evidence from experimental animal models and human retrospective analyses continues to support the use of "hypotensive" or "low-volume" resuscitation in cases involving uncontrollable hemorrhage where immediate and definitive surgical hemostasis is achievable. DCR, DCS, and hemostatic resuscitation all show merit for affording our patients the best opportunity for survivability while minimizing short and long-term deleterious effects. Unfortunately, adequate prospective clinical evidence in human and veterinary medicine is lacking. Pharmaceutical intervention using antifibrinolytics as well as concentrated hemostatic factors may similarly serve a role in treating ATC; however, adequate evidence is also lacking. Regardless of the therapeutic strategy employed, it is imperative to keep in mind that a resuscitative strategy should not be a cookbook recipe, but rather be implemented and adjusted by taking into account the type and severity of injury (blunt versus penetrating trauma) as well as the patient's individual response to treatment. As is practiced in human trauma care, it may also be prudent to develop hospital-specific algorithms based off the patient's mechanism and severity of injury, presenting physiological condition and response to initial resuscitative therapy, in order, to help optimize resource use and improve outcome.

## Diagnostic and Treatment Approach to Acute Traumatic Coagulopathy



**Figure 1:** Diagnostic and treatment resuscitative approach for acute traumatic coagulopathy (information was assimilated from [11, 14, 96]). HR, heart rate; CRT, capillary refill time; FAST, focused assessment with sonography for trauma; PCV, packed cell volume; TP, total protein; aPTT, activated partial thromboplastin time; PT, prothrombin time; TEG, thromboelastography; ROTEM, rotational thromboelastometry; FFP, fresh frozen plasma; CRI, constant rate infusion; SBP, systolic blood pressure; FWB, fresh whole blood; HCT, hematocrit; Hb, hemoglobin; HTS, hypertonic saline.

**Table 1:** Main points for management of patients with acute traumatic coagulopathy

- Primary goal is to rapidly achieve hemostasis
- Utilize FAST to evaluate the abdominal cavity, retroperitoneal space, pleural space, gastrointestinal tract, and fascial planes around fractured bones for areas of “hidden” ongoing hemorrhage that may lead to life-threatening hemorrhagic shock
- Serial measurements (not a one-time measure) of packed cell volume and total protein should be used to facilitate assessing the degree of ongoing hemorrhage
- Use viscoelastic tests to identify the presence of a coagulopathy, predict transfusion needs, and evaluate the response to therapy. When viscoelastic tests are not available, transfuse blood products as needed to maintain PT and aPTT <1.5× of mean normal values
- Incorporate serial measurements of base deficit and lactate in conjunction with traditional clinical values of perfusion (eg, heart rate, pulse quality, mucous membranes, capillary refill time, mentation, body temperature, and arterial blood pressure) as endpoints for evaluating perfusion and the adequacy of resuscitation
- Institute damage control strategy (see Table 2) in severely injured patients with uncontrolled hemorrhage until definitive hemostasis is achieved
- Consider autotransfusion in situations involving acute life-threatening closed cavity hemorrhage when fresh whole blood or stored blood products are not immediately and readily available
- Consider administering antifibrinolytics (eg, tranexamic acid, aminocaproic acid) for trauma-related uncontrolled/noncompressible hemorrhage when viscoelastic tracings are indicative of hyperfibrinolysis. Per guidelines developed for people, antifibrinolytic therapy should be instituted as soon as possible after injury (ie, at least within 3 h postinjury) and should not be administered to patients >3 hours posttrauma
- Patients receiving massive transfusion may require calcium or magnesium supplementation. Monitor ionized calcium and magnesium concentrations in patients receiving massive transfusions as well as following massive transfusions

aPTT, activated partial thromboplastin time; FAST, focused assessment with sonography for trauma; PT, prothrombin time.

**Table 2:** Concepts of damage controlled resuscitation in companion animals

- Permissive hypotension
  - SBP 80–90 mm Hg or MAP 40–60 mmHg (note: traumatic brain injury target SBP > 90–100 mm Hg)
- Hemostatic resuscitation
  - Utilize fresh whole blood (when available) or blood products in a 1:1 ratio of pRBC:FFP
  - Administer cryoprecipitate when fibrinogen <1 g/dL
- Limit isotonic crystalloid use
- Avoid exacerbating and correct any existing hypothermia
  - Core rewarming (eg, warmed resuscitative fluids, blankets, ventilator air, and environment, or forced-air heating blanket)
- Reverse metabolic acidosis (eg, appropriate and timely hemodynamic resuscitation)

FFP, fresh frozen plasma; MAP, mean arterial pressure; pRBC, packed red blood cells; SBP, systolic blood pressure.

**Table 3:** Concepts of damage controlled surgery in companion animals

- Considered in situations in which medical intervention with DCR and noninvasive interventions to control hemostasis (eg, direct pressure, abdominal counterpressure) have failed to control hemorrhage, and that involve the following:
  - Severe hemorrhagic shock
  - Ongoing coagulopathy, acidosis (pH < 7.1), and hypothermia (<34°C)
  - Noncompressible or inaccessible sources of hemorrhage
- The concept of DCS include a 3-tiered approach:
  - Tier 1: *Rapid surgical hemostasis and contamination control*
    - An abbreviated surgical intervention (ideally 1 h or less) to achieve
  - Rapid hemostasis via vessel ligation or cavitory packing
  - Rapid contamination source control
    - Temporary closure with anticipation to re-explore and conduct definitive surgical repair after correction of physiological derangements
  - Tier 2: *Resuscitation*
    - Intensive care stabilization to correct of physiological derangements (eg, acidosis, hypothermia, coagulopathy)
    - Duration depends upon the severity of injuries and patient's response to therapy
  - Tier 3: *Definitive surgical repair*
    - Re-explore with the intentions of achieving definitive surgical repair
    - Pursued once the patient has been adequately stabilized and resuscitated
    - May be conducted within 24–72 hours of initial surgical intervention; however, it may be delayed longer pending the patient's response to Tier-2 efforts

DCR, damage control resuscitation; DCS, damage control surgery.

### Future Studies

Due to the complications ATC imposes on resuscitative efforts as well as the high risk for multiple organ dysfunction and mortality that it carries, it is imperative that veterinarians gain a better knowledge of the prevalence, pathophysiology, and appropriate diagnostic and therapeutic approaches for ATC. Unfortunately, prospective randomized clinical and observational studies evaluating the prevalence of ATC in veterinary trauma patients are relatively nonexistent, therefore, the clinician is left with extrapolating information from current human studies and experimental animal models. To better serve our patients' needs and afford them the best opportunity for survival, studies evaluating the prevalence and etiology of ATC in veterinary trauma patients are warranted. Further, studies are required to evaluate the most sensitive, readily available, and reliable diagnostic tools for detecting coagulopathy early in the course of resuscitation as well as providing evidence-based data to guide directed therapeutic strategies. On the human side, researchers are currently evaluating the role that platelets, endothelial damage, and proinflammatory mediators contribute to the functional scheme of ATC. Therapeutically, further studies on correcting acid-base

disorders, instituting antifibrinolytics (eg, tranexamic acid, aminocaproic acid) as well as different ratios and types of blood products are being investigated to evaluate the optimal goal-directed therapeutic strategy. Considering the dynamic and even time-sensitive nature of ATC, it may be hard to definitively design a standard comprehensive protocol for all patients, but rather an algorithmic approach based on a series of physiological and laboratory findings specific to each individual patient would prove beneficial.

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